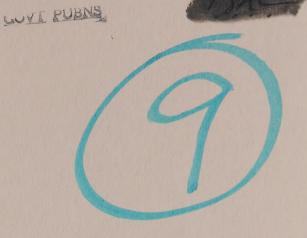
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ROYAL COMMISSION OF INQUIRY INTO CERTAIN DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND RELATED MATTERS.

Hearing held in Court Room 20 Court House 361 University Avenue Toronto, Ontario

The Honourable Mr. Justice S.G.M. Grange

Commissioner

P.S.A. Lamek, Q.C.

Counsel

E.A. Cronk

Associate Counsel

Thomas Millar

Administrator

Transcript of evidence for

July 7th, 1983

VOLUME 9

OFFICIAL COURT REPORTERS

Angus, Stonehouse & Co. Ltd., 14 Carlton Street, 7th Floor, Toronto, Ontario M5B 1J2



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2	DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND RELATED MATTERS.
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5	Hearing held in Court Room 20, Court House, 361 University
6	Avenue, Toronto, Ontario, on Thursday the 7th day of July,
7	1983.
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10	THE HONOURABLE MR. JUSTICE S.G.M. GRANGE - Commissioner
11	THOMAS MILLAR - Administrator
12	MURRAY R. ELLIOT - Registrar
13	
14	
15	APPEARANCES:
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	E.A. CRONK)
17	D. HUNT) Counsel for the Attorney- L. CECCHETTO) General and Solicitor
18	General of Ontario (Crown Attorneys and Coroner's Office)
19	I.J. ROLAND) Counsel for The Hospital for R. DEVINS) Sick Children
20	R. BATTY)
21	D. YOUNG Counsel for The Metropolitan Toronto Police
22	W.N. ORTVED Counsel for numerous Doctors
23	at The Hospital for Sick Children
24	F. KITELY Counsel for the Registered Nurses' Association of Ontario
25	and 35 Registered Nurses at The Hospital for Sick Children

(Cont'd)

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1	APPEARANCES:	(Continued)
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5	G.R. STRATHY) P. RAE)	Counsel for Phyllis Trayner - Nurse
7	M. ROSENBERG	Counsel for Sui Scott - Nurse
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15		(parents of deceased child Jordan Hines)
16	J. SHINEHOFT	Acting for Lorie Pascia and
17	100	Kevin Garnett (parents of deceased child Kevin Pascia)
18		
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/DP/ak

--- Upon commencing at 10:00 a.m.

DR. STEVEN SOLDIN, Resumed

THE COMMISSIONER: Yes, Miss Cronk.

MS. CRONK: Mr. Commissioner,

Dr. Soldin has provided me over the break with a hard copy, if you will, of the slides which he referred to yesterday morning in his evidence, and I would like to propose that they be marked this morning as an exhibit.

THE COMMISSIONER: Exhibit 26.

---EXHIBIT NO. 26: Hard copy of slides presented by Dr. Soldin, July 6th, 1983.

MS. CRONK: The first two slides that he referred to, sir, are reproduced on one page of an extract. I think it can best be identified by - it is page 6 from Therapeutic Drug Monitoring Journal, Volume 3, November 1, 1981. That is inclusive of the first two slides, and the second document is a reproduction itself of the third slide to which he referred and that is described as Figure 1, Theophylline Concentration.

THE COMMISSIONER: Which concentra-

tion?

MS. CRONK: That is the difficultly.

I think it is theophylline. Is that right?

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I think it is themphylling. To ther right?

THE WITNESS: Theophylline.

THE COMMISSIONER: That is spelled ---

MS. CRONK: T-h-e-o-p-h-y-l-l-i-n-e

concentrations.

THE COMMISSIONER: Do they all go in as one exhibit?

MS. CRONK: That would be fine, Mr. Commissioner. Copies have been provided to counsel this morning, sir.

In addition, you will recall,
Mr. Commissioner, the request was made yesterday
by various counsel for Dr. Soldin to reproduce in
a typewritten form the data to which he referred
yesterday in reporting upon the digoxin readings
that he obtained, ante mortem, on the group of
children who had been known not to have received
digoxin and, in addition, the group of patients
who were known to have received digoxin, the two
categories; and in addition the third category of
post mortem testing that he did inclusive of
patients both on and off digoxin.

Dr. Soldin has advised me that in respect of the second category, the ante mortem testing on children, patients who were known to have been on digoxin, the tabulated results of that in



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you first?

fact are set out in the memorandum that was filed yesterday as an exhibit, copy of Dr. Soldin's memorandum to Dr. MacLeod, and that is the only place where those results, I understand, have been tablulated.

in respect of the other two comparative series of tests tabulated. They are not in a finalized form As soon as they are I will have them reproduced and distributed amongst counsel, and marked as an exhibit at that time.

Thank you, sir.

THE COMMISSIONER: Mr. Bogart, are

MR. BOGART: Sir, I do not believe that I have any questions of this witness, but I wish to make one remark, if I may.

THE COMMISSIONER: Yes.

MR. BOGART: That is, as you know, sir, I have shown some interest in a list that was compiled by Dr. Ellis and have gone through it in this evidence at the Preliminary Inquiry, Volume 13, beginning at page 12 to page 35.

My understanding of the transcript, sir, is that he complified 2 lists. One was autopsy



samples and I have been told by Miss Cronk in our meeting yesterday that Dr. Phillips will called in respect of those readings.

In respect to the pre-mortem samples,

I have been told by Miss Cronk that Dr. Soldin is

not the witness who should be asked about these, and
that Miss Cronk is making enquiries of the Hospital
concerning who will be in a position to answer my
questions about the readings that were taken.

On that basis, I have no questions of this witness.

THE COMMISSIONER: All right, thank you. Do you confirm all that?

MS. CRONK: That is correct, sir.

THE COMMISSIONER: Thank you.

Mr. Strathy?

CROSS-EXAMINATION BY MR. STRATHY:

Q. Doctor, I would like to begin by asking you about the methodologies for the detection of digoxin that we have been hearing about.

To date I think we have heard of three methods: the RIA method; the FPIA method and the HPLC method, if one can call it that at this point.

Let me start with the RIA method. As I understand it, sir, it has been in use generally





of that?

in North America for about 10 years and at the Hospital for Sick Children since about 1974. Am I right?

- A. That is corect.
- Q. If you could have Exhibit 25 in front of you, that was your memorandum to Dr. MacLeod.
 - A. Yes.

MR. STRATHY: Mr. Commissioner, do you have a copy of that?

THE COMMISSIONER: Yes, I have, thank you. I am very well treated now. I have this book with all the exhibits in it.

MR. STRATHY: Q. Looking at the last page of that memorandum. I gather, Doctor, that that reflects a survey that was done of a number of laboratories in North American concerning their results of digoxin testing? Quality control samples are sent out to each laboratory and analyzed and then the results tabulated in this format.

- A. This is a survey that is done on a monthly basis.
 - Q. Who is it that does the survey?
- A. The American Association for Clinical Chemistry the Therapeutic Drug Monitoring Program for that Association.
 - Q. And your Hospital is a member



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Α.	We	subscribe	to	that	program
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- Q. Are the laboratories to which these are sent, or the tests are sent from, are they all hospital laboratories?
- A. No. Some would be private laboratories any laboratory offering digoxin analysis
 could subscribe to this program. The majority are
 probably hospital laboratories.
- Q. Looking at the bottom left hand corner of this chart, Exhibit 25, do you have that in front of you?
 - A. Yes bottom left hand corner?
 - Q. Bottom left hand corner.
 - A. Yes.
- Ω . It appears to indicate that RIA is in use at the present time at least by the vast majority of the laboratories that contributed to the survey?
 - A. Right.
 - Q. In fact, some 312 of the 404?
 - A. Yes.

THE COMMISSIONER: I would like to know how you calculate that - how you figure that? Am I looking at the same chart?

MR. STRATHY: Mr. Commissioner, it is the last page of Exhibit 25, in the bottom left hand corner.



25

THE COMMISSIONER: Yes, yes, I

understand.

MR. STRATHY: There is a reference to all labs, 404.

THE COMMISSIONER: I was looking at the wrong chart. Thank you.

MR. STRATHY: And 312 of those are using RIA.

Q. Now, as I understand it,

Doctor, the RIA technique was developed and designed

for the therapeutic monitoring of digoxin in a

clinical setting. Am I right on that?

A. That is correct.

Q. That was when it was invented, if you will, in 1969 or 1970?

A. Yes.

Q. That was the purpose of the invention, and that is the use to which it has been put since that time.

A. Mainly, yes.

Q. And we have, as we have seen, these kits which are designed for that very purpose?

A. Right.

Q. And the Hospital for Sick
Children, instead of using a kit, instead of buying



the same?

the cake mix, you make your cake from scratch, basically?

- A. Right.
- Q. But the principles are exactly
- A. Yes.
- Q. I take it from your evidence that you essentially consider the RIA method to be a realiable and useful method for the purposes for which it was designed?
 - A. I do.
- Q. And perhaps the only qualification you would have to that is that it perhaps may not be as specific as it might be with respect to the detection of substance X.
- A. That is correct. I think one has to have another either, provided it is appropriate, the test is appropriately done, and there is also the reliable, in my opinion, by the RIA technique.

As you will note, in the handout that you are referring to, there are many labs that appear to be performing poorly, and they are also using the RIA technique, so that is another factor.



BMB.jc

Q. So, just looking as you point out then to the bottom of the page under RIA, you have some labs using that technique reporting as low under the column "Min", as low as .42 and other labs reporting as high as 11.79?

A. That's right.

Q. When, according to this, the target, what they should have found in the perfect world would have been 3.80?

A. Correct.

Q. So, what you're saying is, there can be a tremendous variation in the results if the test is not properly administered?

A. That's right, yes.

Q. But I take it you agree with me with the further qualification that it's not as specific as it might be with respect to Substance X?

A. Yes.

Q. And if I can put it in somewhat imprecise terms, I take that when you are using an immunoassay procedure, one of the things that you want is specificity. Specificity equates to good in terms of immunoassay, it's a good thing?

A. Right.

Q. The less specific the assay is, the more it's possible that it will pick up things



B.2

other than the substance for which it is designed?

A. Yes.

Q. Now, turning then to the second methodology that you have I think been the first witness to give any significant evidence about, FPIA. As I understand it, Doctor, the FPIA, or the Fluorescence Polarization technique is something that has been used in biochemistry for some considerable period of time. Not in terms of digoxin, but the technique itself?

A. Yes.

Q. Can you give us an idea of how long it has been in use?

A. Approximately 50 to 60 years. The thoughts were first written down some 50 to 60 years ago.

Q. So, it's a technique that chemists or biochemists such as yourself are familiar with and have used for some time?

A. It's a technique that some people have used for some time, yes.

Q. You are qualifying that. I take it you haven't used it for some time?

A. That's correct.

2. But I gather from what you have



said, it is only reasonable that the test has been defined or developed for purposes of digoxin?

A. For the purposes of drug analysis, measurement of drug concentrations by digoxin, being one drug is just part of the spectrum.

Q. So, is it in recent years the detection has been used for drugs?

A. Yes, in the last four years perhaps.

Q. And the Hospital for Sick
Children has now had FPIA for digoxin for about four
or five months?

A. Three or four months, yes.

Q. And I gather very soon you are going to be doing all your digoxin testing using this methodology?

A. I think in two to three weeks probably, yes.

Q. Now, is it fair to say that this FPIA method is also designed and intended for the therapeutic monitoring of digoxin in a clinical setting?

A. That's correct.

Q. And I take it from your evidence that you consider it to be a reliable and useful



B.4

procedure for the detection of digoxin in that setting?

A. That's correct, yes. It is the state of the art, perhaps.

Q. I take it from that that you mean, and I have gathered from your evidence, that you consider it perhaps to be a somewhat better procedure than RIA, both in terms of its efficiency and in terms of the precision of its results? I don't want to take you too far on that point because --

A. They are both good procedures

I think. I think we went into this yesterday. I

have some slight preference for the FPIA method, yes.

Q. Do I understand correctly from your evidence that it, like the RIA, has the same problem with respect to Substance X, that is that there is a specificity problem and even FPIA may show up Substance X?

A. Yes.

Q. But perhaps not as much as the RIA method?

A. Right.

Q. Now then, turning to HPLC. I understand from your evidence that you yourself have never used that for digoxin?

A. I have never used it for digoxin.



:B.5

Q. But looking at your curriculum vitae, and I won't ask you to pull it out, but it does seem to me as though you've had considerable experience with HPLC in the clinical setting?

A. Yes.

Q. And just to be sure that I understand, there are references to a number of articles that you've written, lectures that you have given pertaining to HPLC, and sometimes it is referred to as High Performance Liquid Chromotography. Is that the same thing as high pressure?

A. The same thing, right.

Q. So, you do have a considerable, if you will, and it's an expression I don't like, but hands-on experience with HPLC?

A. Right.

Q. Now, as I understand it, and I'm going to put this in fairly simplistic terms, but as I understand it, HPLC involves two sets. It involves firstly a separation procedure where you separate out the substance which you wish to analyze. Is that an accurate statement?

A. One performs any chromographic analysis essentially to separate the components of a mixture. So, you have several things and you wish to separate them.



B.6

			Q.	And the	thing	that	you	separate
off	is	called	a	fraction?				

A. Well, you can collect fractions from the common element.

Q Perhaps if I can tell you what I understand the second step to be and you can perhaps put the whole thing in context. I was going to say that having done the first step of separating, you then measure the thing that you have separated off?

A. Right. In other words, first you separate the compounds and then you have to detect the compounds. So, you need a detecting device at the end of the common ...

Q. Now, when you talk about detecting, are we talking about the detecting levels in the same way as we have in HPLC - I am sorry, in the same way as we have in RIA?

A. Yes, detecting concentrations of a drug. It is a better word than levels.

Q. All right, fair enough. So, there is basically then a two-step process, a separation and the detection of concentrations?

A. Right.

Q. I believe you were present in the room for the evidence of Mr. Cimbura?



B.7

А

A.	For	most	of	that	evidence,	yes.
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Q. Well, I wonder if you heard his evidence with respect to the procedure that he used concerning HPLC. Let me at least put to you what I understood his evidence to be. As I understood what Mr. Cimbura did, it was that he did the first step, that is, he used HPLC to perform the separation but he did not then go on to use that same methodology for detection, he used RIA for detection?

A. Well, you cannot use HPLC for detection, you have to use some form of detector. Now, there are other different types of HPLC detectors.

One would be RIA, okay, at the end of the procedure.

Q. Well, do I understand it then that an HPLC method would have its own type of detector or would you simply couple it onto some other detector system?

HLPC procedure, one looks at the molecule that one wishes to identify, quantify, and makes a decision as to what type of detection system would be most appropriate. It may mean that one would want a fluorescent detector or a spectrophotometer or an electric chemical detector, or maybe, as Mr. Cimbura chose to use, a radioimmunoassay as a detecting device essentially.





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Q. So that having gone through

HPLC then, there are a number of different detection

devices that you can employ?

A. Yes.

Q. Now, as I understand it, HPLC never has been in use at the Hospital for Sick Children for the monitoring of digoxin?

A. No.

Q And you can look at our chart on Exhibit 25, it appears that there was one laboratory using HPLC, at least one laboratory responding, providing the information - one laboratory using HPLC. Am I right about that?

A. You're right, yes.



C/DM/ak

	Q.	And	do	you	happen	to	know	which
laboratory	that was?							

A. No, I don't.

Q. You don't know whether it would be Mr. Cimbura's laboratory?

A. I don't know. I am not - I don't - I assume that he wouldn't be a member of this program, this is a program for clinical laboratories and not for forensic laboratories.

Q. All right. Looking in any event at those figures beside that HPLC under column "Min" and "Max", it would appear that that laboratory simply submitted one response that its finding was 6.40.

A. Correct.

Q. When it should have been a finding of 3.8?

A. Yes.

Q. So in that particular case there was a fairly wide variance from the target using HPLC?

A. Correct.

Q. And I suppose you can't really tell us whether that was due to the method itself or the skill with which it was performed?

A. No, I have no comments to make



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on that. Other than that I personally would never use HPLC for the routine monitoring of digoxin in any hospital laboratory at the present time.

- Q. And I gather from your evidence there were several reasons for that. One being that it is a very time consuming procedure, is that right?
- It is time consuming. The protection devices they are simple, and that are available and they lack sensitivity.
- 0. I am sorry, what was that about sensitivity?
- The detection devices that are available lack the type of sensitivity that is required in order to do therapeutic drug monitoring easily and rapidly on patient samples.
- You mean the detection methodologies to be used with HPLC lack the sensitivity?

A. Correct.

THE COMMISSIONER: I am sorry, you lost me. I thought we didn't have any detection devices with HPLC?

THE WITNESS: No, those devices that are used together with HPLC. HPLC is used in



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the first step to separate digoxin from the other compounds and you can detect it. If you use a spectrophotometer, we say the sensitivity is not appropriate for clinical samples. So you could choose RIA which was the choice of Mr. Cimbura and that certainly is a sensitive procedure. That then would mean that every sample has to be analyzed both by HPLC followed by radioimmunoasay and it is very time consuming and it just doesn't lend itself to the routine monitoring of digoxin in a hospital laboratory.

It is important in our clinical setting to ideally get a result back very quickly so that appropriate changes in the doses regimen can be made.

MR. STRATHY: 0. Just so I am sure of this. You talk about the detection systems and you mentioned a spectrophotometer I believe. Is it fair to say that RIA is not usually used as a detection system with HPLC?

- It is sometimes used, but rarely.
- What would you more often be using with HPLC?
 - Α. The most common detector is a



spectrophotometer, then fluorescence probably the next most common, and electrochemical, the third most common.

Q. Thank you. Now, I gather that HPLC suffers from the same problem with respect to substance X as FPIA and RIA do. Let me start with a question on these. As I understand it with HPLC you can only separate out two substances, or three substances if you know to begin with what those substances are? In other words, you have standards of various substances and you run them through the system to begin with.

A. I think with HPLC you can carry out separation of compounds, they may be known and they may be unknown. You wouldn't be able to identify the unknowns unless you have a standard.

Q. All right. So if you were trying to separate out digoxin from substance X you would have to have a standard for substance X before you did that, before you could do that reliably? You can't be sure that what you have coming off is only digoxin and not digoxin and substance X unless you have been able to identify substance X and run it off?

A. Yes. Let me answer that



question, this is a hypothetical question.

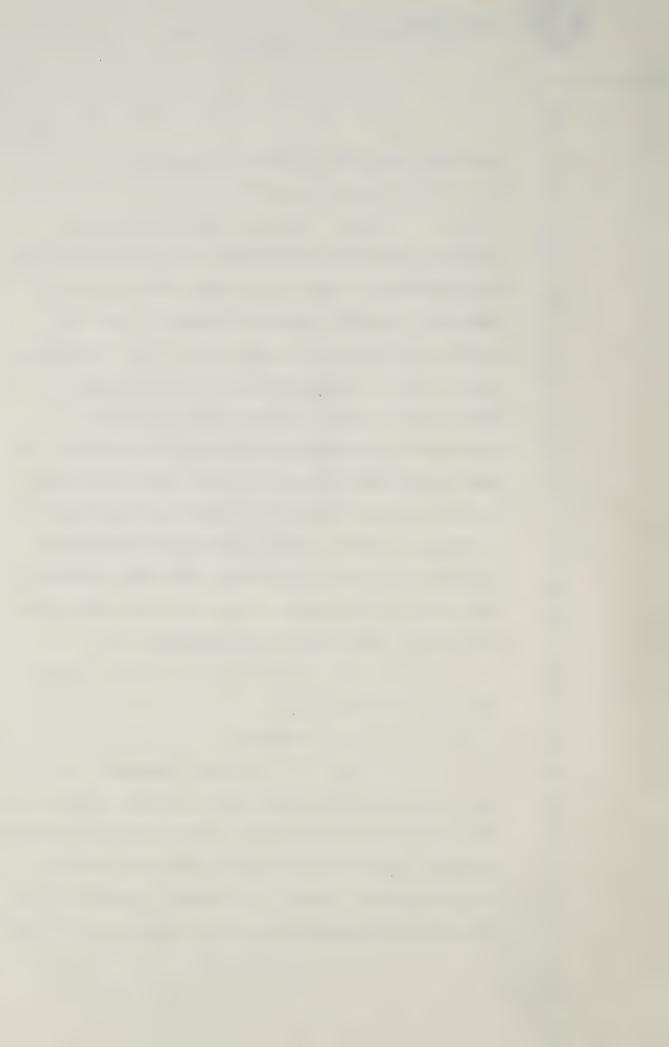
Q. Yes.

injecting into the chromatogram a mixture of digoxin and substance X, and let us assume that they are separated under the system of analysis that we chose to use in the chromotography. We would then get two peaks eluding from that column, right, which could be identified and they could be identified by the radioimmunoassay for example. So that way we would be able to show under this hypothetical sample that one of those peaks corresponds to digoxin, and the other peak doesn't correspond to digoxin but does cross-react with the antibody. That would be a stronger indication that that other peak is the compound we are interested in.

Now, at this point in time we don't have a standard ---

Q. Exactly.

A. --- for that compound. So if they separated and if one could identify these two peaks with our detecting system whatever detector we chose, then we would be in a good position to carry on further studies to attempt to identify the structure of compound X, or substance X, but if they





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didn't separate, which is the next step, then you would have no way of saying that the HPLC system with RIA detection has in fact separated substance X from digoxin.

- So you are talking purely in a hypothetical sense then?
- Right. Α. In my opinion in order to achieve that identification, assuming substance X was very similar to digoxin and ran identically with digoxin in the chromatogram, one would have to use a different detector.
 - A different detector than? 0.
- Α. Than radioimmunoassay. So the detection system that would have to be used in my opinion would be mass-spectromotry, and if you combined HPLC with mass-spectromotry you could then with certainty say that that alluding peak is or is not pure digoxin. You would also, in my opinion, be able to identify substance X quite quickly.
- So what you are telling us then is, and I gather what you have given us is reasonable shorthand of what you would actually do. What you are telling us is that there is a way in which you as a biochemist would go about using HPLC and massspec to separate out substance X from the digoxin in



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any particular sample? There is a way it could be done?

- That is the way I would approach this problem.
- 0. If you were in the race to find substance X, is that correct?
 - That's correct. Α.
- 0. But as yet, as I understand it, no one has done that using HPLC?
- At the present time no one has done that.
- So at least presently using the HPLC method as it has been used, we have heard from Mr. Cimbura, it has not been possible to separate out substance X from digoxin because we haven't gone through the procedure that you have described?

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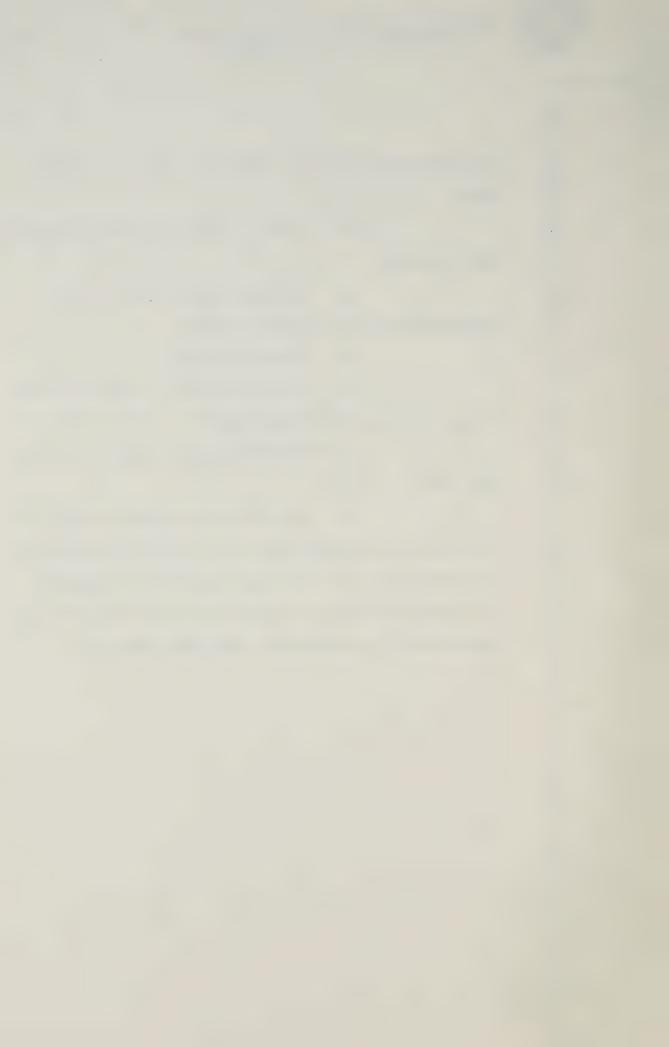
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Well, to my knowledge no one A. has - there are some studies, I must retake on this there are some studies that I have heard coming out from Dr. John Gault's laboratory.

> Q. John who?

Gault.

And that is G-a-l-t?

G-a-u-l-t, in Newfoundland in which I have been led to believe he has managed to separate, by HPLC, digoxin from another compound. This is hearsay, I have not spoken to Dr. Gault myself on that particular issue.

0. Do you know what the other compound is?

> A. No.

Once you had gone through this procedure of yours that you have described, would it then be possible to develop a standard for Substance X that could be routinely run through HPLC?

If we could identify its structure and if we could then purify it we would have a standard which could then be used.

That would make the detection excuse me, the separation of digoxin using HPLC considerably more reliable?



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		A.	Well, you would then be able
to	identify	where it	ran chromatographically. Di
it	run with	digoxin?	You would be able to attemp
to	separate	the two.	

Q. With some considerably more precision than would be possible at present?

A. It would be a lot easier, yes, if you had a standard.

Q. Now, I do not want to spend a great deal of time on this, but since we are speaking of methodologies for the detection of digoxin, if you can look again at the last page of Exhibit 25 there is also reference to an EIA in the bottom left-hand corner which I gather is enzyme immunoassay?

A. Enzyme immunoassay, yes.

Q. Is that a similar procedure to RIA, in general terms?

A. It is somewhat different. It also has antibody reactions.

Q. And then at the bottom there is FIA. What is that?

A. Fluorescence immunoassay, and it is again similar, but also has some antibody involvement.

Q. Just out of interest, that



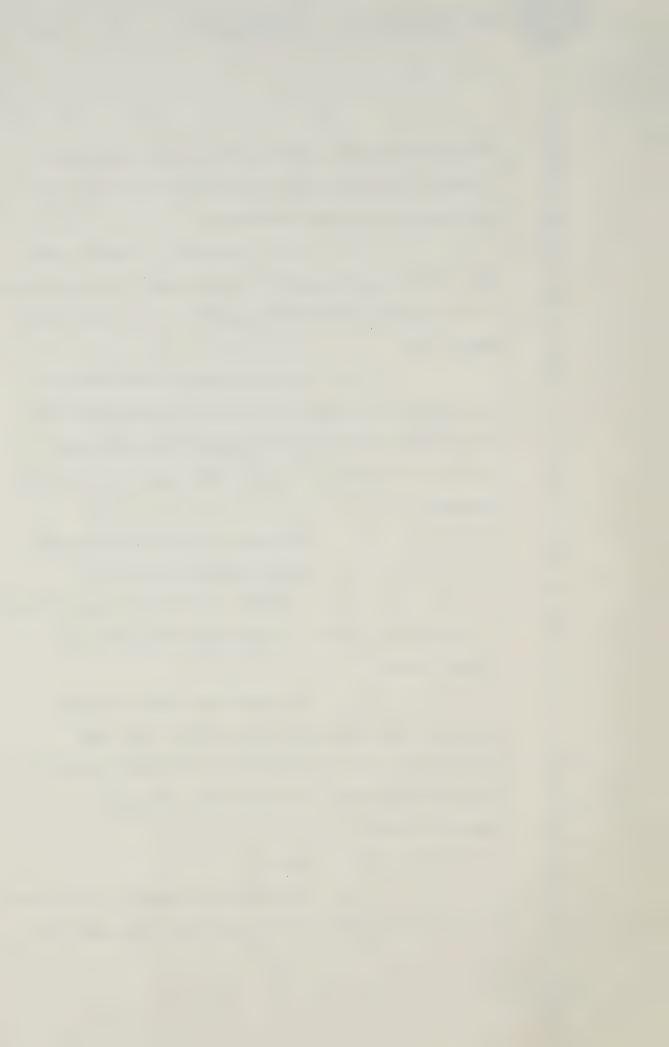
procedure seemed to produce the least deviations.

Is there anything about that system that makes it very specific or very accurate?

A. It is probably - I have never used the FIA procedure for digoxin and it does appear in this particular month's report to have performed rather well.

Q. And speaking of performance, am I right that where it says in this report, near the bottom, two-thirds of the way down the page, your result was 3.5. Is that the Hospital for Sick Children?

- A. On that particular month, yes.
- Q. Using which, FPIA or --
- A. RIA. We have not yet switched we are not one of the 35 labs reporting the FPIA in that month.
- Q. You have mentioned in your evidence, both today and yesterday, that mass spectrometry is one method that you would consider highly reliable for the detection of digoxin concentrations?
 - A. Yes.
- Q. My understanding of that method is that it is certainly not one that you would use



in a therapeutic context, on a regular basis at least?

A. That is correct. It requires very expensive equipment. The combination of a liquid chromatograph and a mass spectrometer, you are talking of something around \$350,000 and you could only measure a few samples a day.

A routine laboratory gets 20 or 30 samples every day for digoxin, at least ours does, and you could not possibly apply that method to all the samples we get.

Q. I gather that mass spectrometry is a method that uses the - I am going to put this badly because I am going to try to put it in very simple terms, but it works on the molecular weight of substances?

- A. Mass spectrometry?
- Q. Yes.

A. What happens is, the molecules get broken down and the fragments can then be identified. Digoxin will break down very characteristically. There is a characteristic breakdown pattern for every compound that exists and therefore you can identify - fingerprint that molecule with a mass spectrometer, very specifically.

Q. And you feel, using a mass





spectrometer, that you could separate digoxin from Substance X?

A. I have not done that, but I feel that that is probably the route. It may not separate chromatographically but even if it does not separate chromatographically one will be able to subtract the digoxin spectrum from Substance X spectrum and therefore identify Substance X.

Q. Are you in the race for the identification of Substance X?

A. I am interested in identifying Substance X, yes. I do not know that I am in a race. I am interested in identifying this compound.

Q. Are you looking for funding to finance it?

A. We would like funding, yes.

MR. STRATHY: Perhaps you could speak to the Commissioner.

THE COMMISSIONER: I am already in trouble.

MR. STRATHY: Q. Doctor, let me ask
you some questions for a moment about your methodology, and I recall from your evidence yesterday that
all the sampling that you are talking about that you
did was with respect to blood, whether it be plasma
or serum. Is that right?



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Q. And that blood is what you use in your day-to-day monitoring in the Hospital?

For most drugs. Occasionally we would use saliva but for most drugs we use blood, yes.

Again, all the work that you Q. did, at least as a routine basis, was on samples from living children and not as a routine matter, certainly, on post mortem samples?

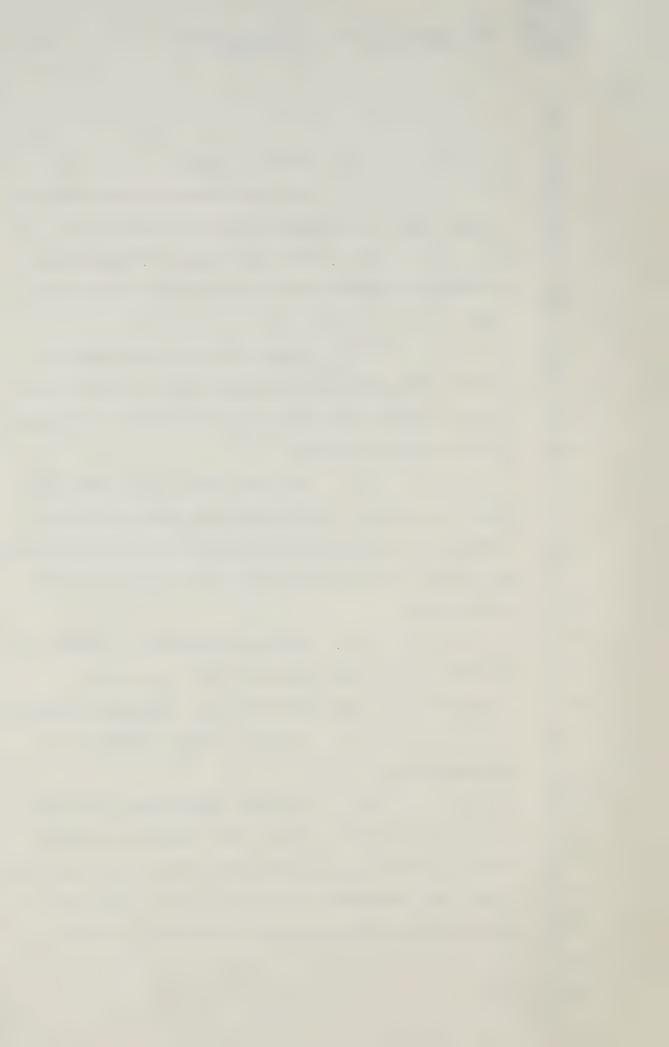
The Hospital has an instruction that all autopsy samples are analyzed on a routine basis, so I would have to say we do routine ante mortem, of course; we are compelled to do routine autopsy monitoring.

Q. You say compelled. I take it that is not something then that you really consider to be your bailiwick as a climical biochemist?

I think I would prefer not to be doing that.

> Q. Is there some reason for that?

Well, I am trained in several One is as a clinical biochemist and that means that I am interested in patient care. Once the patient dies there is nothing I can do for that



particular patient. I think samples should then probably be sent to forensic laboratories at that point in time.

Q. The procedures that you have mentioned you use on living patients, you have indicated were specifically designed and intended for use in just that setting, the clinical therapeutic setting. Do you have any reservations about using those methodologies on the post mortem samples that are provided to you in the autopsy context?

A. Well, I would have the reservations that any scientist would have who has read the data that we are aware of, that is, does Substance X, if we call it that, if released after death would it contribute to the possible measurement by either RIA or FPIA or whatever procedure?

In order to answer those questions, one really has to develop this mass spec method and we can then address that issue, but until we know what we are measuring in post mortem samples we cannot address that issue.

Q. That, it seems to me, is a very critical point that you have raised, and I gather from what you are saying that you cannot say,



at this point in time at least, whether Substance X is in fact released post mortem, on the basis of the current scientific knowledge about it?

A. I can only share my experience with you. We have measured a digoxinlike compound, whether it be Substance X or whatever, in some autopsy samples, in patients that were never receiving digoxin.

THE COMMISSIONER: In patients who were never receiving --

THE WITNESS: In patients who were never receiving digoxin.

MR. STRATHY: Q. So --

A. At least according to the medical records.

Q. Are those patients in the category that we have been talking about previously, that is, less than three months of age?

A. No, some of them are older. In fact, the highest reading was obtained in a close to five year old infant.

Q. The evidence we have heard,
I believe so far, is that Dr. Seccombe's findings of
Substance X were zero, after three months of age?

A. He did not look at post mortem samples, I don't think.



age?

	Q. No, you are quite right. So
we	know from Dr. Seccombe that it may exist pre-mortem
up	to three months of age. What you are telling us
is	that your studies show that it may exist post mortem
in	other children?

- A. Correct.
- Q. Even older than three months of
- A. Right.
- Q. How many children did you test, post mortem?

A. We have done a lot of autopsy samples and, again, I would prefer the autopsy data to be handled by Dr. Phillips, but I can share some of our experience with you.

The total number of post mortem digoxins that we have done at the Hospital between March 24, 1981 and April 24, 1983 is 520, and during that time period there were nine patients that we are aware of that had never received digoxin and that had measurable digoxin concentrations, using the RIA technology. The highest result was 2.1 nanograms per millilitre, in that particular series.

- Q. That is in serum, is it?
- A. In serum or plasma, yes.



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Q. Are you able to give us any breakdown in terms of the ages of those nine patients?

A. I have it here, yes. I would be quite happy to make this document available to you, should you so wish.

MR. STRATHY: I wonder, Mr. Commissioner, if I could just see it for a moment. Do you mind if I just confer with the witness for a moment to try to understand some of this, as it were, off the record?

THE COMMISSIONER: It is a bad habit to get into, but --

MR. STRATHY: I will put it on the record.

THE COMMISSIONER: Yes, all right.

MR. STRATHY: Q Do I understand it, Doctor, that these nine that we have here are the nine children who had not been receiving digoxin, in which you detected digoxin levels at post mortem?



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this list by	Dr. Phil	llips	. This	isn't	my	list	:, I
naven't compi	iled it,	Dr. I	Phillips	has.			

All right, before we go any Ω . further then, do I understand, Mr. Lamek, perhaps you can help me, Dr. Phillips will be called and that the other data that accompanied this list will be introduced at some point?

MS. CRONK: Yes, Mr. Commissioner, we have already indicated that we will call Dr. Phillips when available to testify as to the autopsy results including, as I understand it, these nine children.

> THE COMMISSIONER: All right.

MR. STRATHY: Thank you very much, Miss Cronk. I do propose that this be made an exhibit but if I can first just take you through it briefly, Doctor. It indicates, it seems to me, that in the nine children that fell in that category, there were ranges observed between 1.0 nanograms per millilitre and 2.1 nanograms per millilitre.

> THE WITNESS: That is right.

MR. STRATHY: Q. And the age of the 2.1 nanograms per millilitre was approximately five years, as you have already indicated.



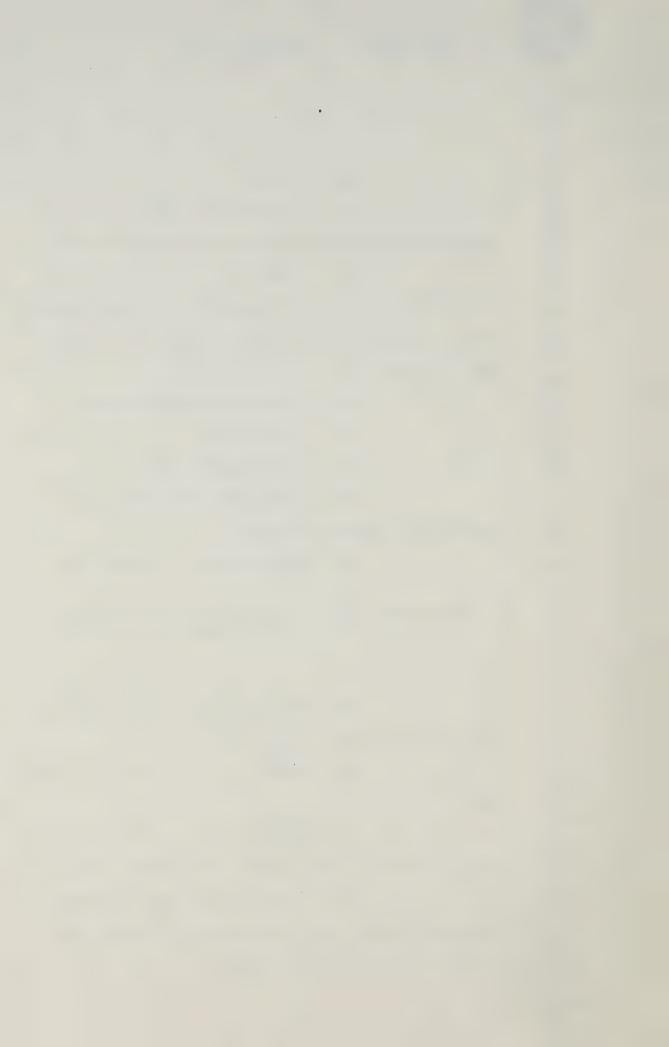


1 2 Right. Α. 3 And the ages seem to range 0. between virtually new born to five years of age. 4 A. Yes. 5 It appears that in at least six 0. 6 of the cases, the children had been on Ward 7G. 7 What is 7G? 8 It is our Neonatal Ward. 9 I'm sorry? Q. 10 Our Neonatal Ward. Α. All right. May this be 11 Q. entered as the next exhibit? 12 THE COMMISSIONER: Exhibit No. 27. 13 14 ---EXHIBIT NO. 27: Chart - re Age of Nine Children. 15 16 THE COMMISSIONER: You don't mind 17 parting with this, or do you? 18 THE WITNESS: If I can get a copy 19 back. 20 THE COMMISSIONER: Yes, all right. 21 Well, I think we can probably get copies back.

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Neonatal doesn't mean premature, it means just close to birth, is that right?

May I just ask this one question.



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THE WITNESS: Right.

MR. STRATHY: Ω . I take it that you're not able to tell us with respect to these nine children whether these levels existed pre-mortem?

A. No.

Q. So, really, what you are telling us is that based on your research there is a possibility at least that substance X is released post mortem?

A. There's a possibility, yes.

Q. And this is something I take it you want to pursue further as well?

A. Yes.

THE COMMISSIONER: Unless of course it is digoxin that's released post mortem?

THE WITNESS: None of these children were known to be on digoxin.

THE COMMISSIONER: No, no, but it's a substance that's released.

THE WITNESS: Unless there is endogenous digoxin.

THE COMMISSIONER: The substance could be digoxin, couldn't it?

THE WITNESS: Could be, yes.

MR. STRATHY: Ω . I suppose the



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other possibility too is that for some reason they were administered digoxin and it wasn't recorded? That's the other possibility. Q. All right. These samples that were taken with respect to the nine children we've just mentioned, were they taken within a reasonably short time after death? Do you know when they were taken? A. I don't have the times. I don't know if they're on that, time of sampling relative to time of death. I'm not aware of that. Dr. Phillips would have that. 0. So, you don't know when the samples were taken? Unless it's on that list, I A. don't know. THE COMMISSIONER: I don't see it on here. THE WITNESS: But Dr. Phillips would have that data. THE COMMISSIONER: I don't see anything there that would be of any help. THE WITNESS: It's not on there.

MR. STRATHY:

as a routine matter when would an autopsy blood

Q. Can you tell us





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A. Well, it would be variable.

It depends on the length of time it perhaps takes
to get parent consent. It might be a few hours to...

Q. Let me ask you this, Doctor.

We have heard in previous evidence that with respect to blood serum levels, there is what has been described as a multiplier effect between pre-mortem and post mortem levels. Is there, in your view, a possibility that this same multiplier effect may take place with respect to substance X?

A. It's a hypothetical. It may occur.

- Q. It's a possibility though?
- A . It's a possibility.

THE COMMISSIONER: Probably we've had this, but these were autopsy babies that you were examining for digoxin, is that right?

THE WITNESS: Yes.

THE COMMISSIONER: But I understood an autopsy of course will only be - it is only rare occasions that there will be an autopsy. There's not an autopsy automatically on the death of a baby, is there?

THE WITNESS: No, there isn't,





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you're right. THE WITNESS: Right. tested all babies who died for digoxin? autopsy ---THE COMMISSIONER: better look it up? March of 1981 on tested for digoxin?

THE COMMISSIONER: There is? THE WITNESS: No, there isn't. THE COMMISSIONER: There isn't. THE COMMISSIONER: Well, did I not understand that as a routine the Hospital had THE WITNESS: Well, certainly all Which is the right pronunciation, autopsy or autopsy, or had I THE WITNESS: Well, ---THE COMMISSIONER: Well, autopsy, that's your pronunciation, and you are a lot more familiar with it than I am, but it is not true then that the Hospital had all babies who died from THE WITNESS: There are people that could answer that question better than I can. THE COMMISSIONER: Well, would the 500 that you mentioned, you said you did 520, that is 520 tests that you did and there may have been fewer than 520 autopsies? Is that right? 24



			THE	WITNES	SS:	Well,	in f	act,	on	
this	list	that	Dr.	Phill:	ips ga	ave me,	this	is	anoth	ner
list	that	you o	don't	have	yet,	the to	tal r	umbe	er of	
post	morte	em exa	amina	tions	durin	ng that	same	per	iod v	was
705.	So,	not e	every	post	morte	em exami	inati	on h	ad a	
digo	xin ar	nalys:	is do	ne ove	er tha	at perio	od.			

THE COMMISSIONER: Well, some day we'll get that cleared up.

MR. STRATHY: It sounds as though it's going to come in through Dr. Phillips, so, perhaps we can defer.

- Ω. Just one point of clarification on that subject though, Doctor. In your testing of these samples, did you have some instances where children who had not been administered digoxin had no concentrations of digoxin detected?
 - A. Oh, most definitely.
 - Q. All right.
- A. So, in many cases, there was no record of digoxin and the results obtained was less than 0.5 nanograms per millilitre.
- Q. And I take it in a number of other cases you had children who had been receiving digoxin and therefore you did detect digoxin levels in those children?



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A. Right	
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- Q. And all the results are available in some published form of which the last exhibit is just a part?
- A. And if they're not Dr. Phillips
 I'm sure can make them available.
- Q. All right, thank you. So, there is some body of data somewhere?
 - A. There is, yes.
- Q. I think we got into this area when I was asking you about your work on blood and I just want to be sure, I think you confirmed it already, that none of your work, whether it was pre-mortem or post morten was with respect to tissue.
 - A. Yes.
- Q. And would you agree with the evidence of Dr. Ellis that one could develop a method for using RIA on tissue but it would take some months at least to develop it?
- A. It would take a time period of several months, yes.
- Ω. I'd like to turn to a different area, and perhaps you could have Exhibits 15B and C placed in front of you and also perhaps Exhibit 24;



24, 15B and C.

We have had, Dr. Soldin, Exhibits 15B and C identified as part of the Therapeutic Drug Monitoring Program and, as I gather from our discussion yesterday, the Hospital for Sick Children is one of the few hospitals in Canada that has something described as a Therapeutic Drug Monitoring Program?

- A. Right.
- Q. And one of the either two or three in Ontario that have that sort of program?
- A. I'm not aware of any other hospital in Ontario that has this.
- Q. I'm sorry. So, as far as you know, you are the only hospital in Ontario?
 - A. Right.
- Q. Now, you testified yesterday that the therapeutic levels for digoxin are, in your view, 0.8 nanograms per millilitre to 2.0 nanograms per millilitre?
- A. Those are the concentrations of digoxin that are probably therapeutic.
- Ω . As opposed to probably subtherapeutic and probably toxic, is that right?
 - A. Yes.



2 3 4 5 6 that? 7 8 Exhibit 15B. 9 10 back of mine. 11 12 got the front copy, sir. 13 14 15 16 17 What does it say, I'm sorry? 18 MR. STRATHY: 19 20 approach."? 21 22 23 shows the level in the column that called "Therapeutic

Q. And if you look at the back of Exhibit 15B, at the very bottom, it says: "General guidelines for therapeutic drug monitoring." THE COMMISSIONER: Where do you see MR. STRATHY: It's the back of THE COMMISSIONER: It's not on the MR. STRATHY: Well, maybe you only THE COMMISSIONER: I see. Well, perhaps the back has a second page. MR. STRATHY: It could be. It is I believe on the form itself, it is on the back. THE COMMISSIONER: Yes, all right. At the very bottom. "Some patients THE COMMISSIONER: may require a more individualized MR. STRATHY: No, just the one above that where it says "Digoxin", and there it

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1 2 Range", it shows a level of .8 to 2.0. 3 Q. I understand that that letter is 4 a Greek letter mu, is it? 5 Right. Α. Q. And that stands for micrograms? 6 Right. Α. 7 Q. Micrograms per litre translates 8 to nanograms per millilitre? 9 Correct. Α. 10 THE COMMISSIONER: Not dead on. 11 MR. STRATHY: I beg your pardon? 12 THE COMMISSIONER: Not dead on. MR. STRATHY: Well, as I understand 13 it, it does. Where we get into trouble is with 14 moles. 15 THE WITNESS: It translates exactly. 16 THE COMMISSIONER: Oh, I see, all 17 right. 18 MR. STRATHY: Since there are 19 1,000 millilitres in a litre and 1,000 nanograms in microgram, it's the same. 20 THE WITNESS: Yes. 21 MR. STRATHY: Q. So, is that what 22 you had in mind when you gave us those figures of 23 .8 to 2, is that the reference? 24



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A. Yes,	that's	the	reference
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Ω. And the same appears on Exhibit 24, which you don't need to put in front of you, but it is the TDX data sheet on digoxin, I believe it specifies the same range.

THE COMMISSIONER: You say Exhibit 24?

MR. STRATHY: Q. Exhibit 24. Do you have that in front of you, Doctor?

A. Yes, I do.

 Ω . I believe that level is set out in that exhibit. I'm just trying to find the reference.

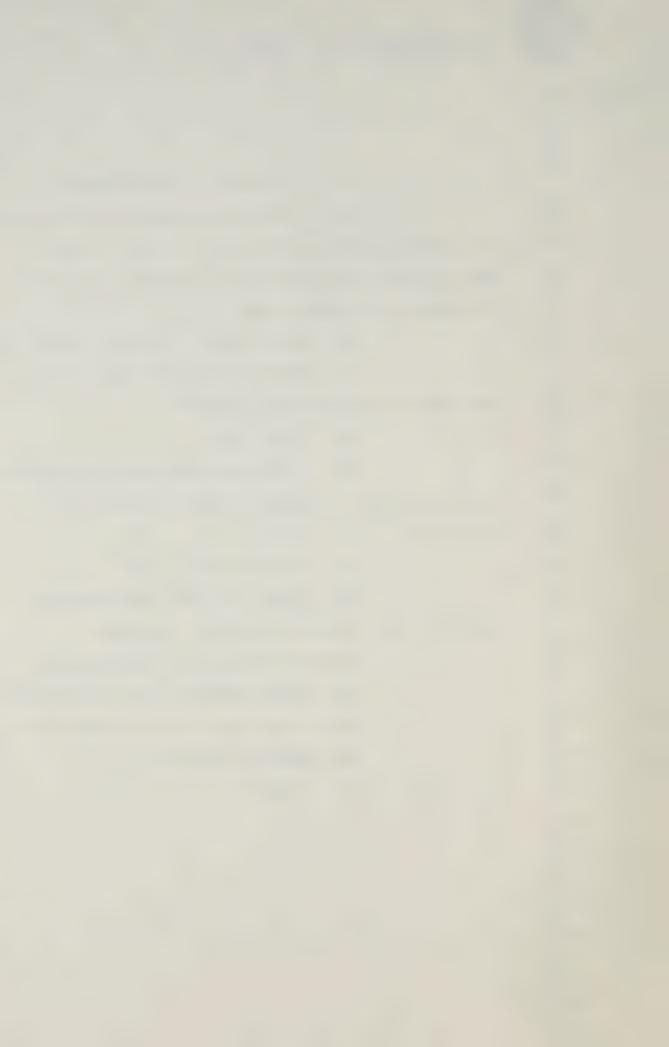
A. It's on page 17.8.

Q. Page 17.8, the top paragraph

where it says "Expected Results". It says:

"Optimum therapeutic level affects are usually observed when serum levels are in the range from 0.8 nanograms per millilitre to 2.0."

A. Right.



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Q. Is this document, Exhibit 24, the source document for the references?

A. No, no. Document 24

didn't exist when these requisitions were styled

and developed. We had, and I had many discussions

with the clinical pharmacology group at Sick

Children's and it was their experience, as well as

some, many papers in the literature, that this

would be an appropriate therapeutic range. The

American Association for Clinical Therapeutic

Drug Monitoring Program, in fact, recommends

that range and they have published a little

booklet which I have here which provides that

range, this was one of the source documents.

Q. So were you one of the people responsible for the preparation of Exhibit 15-B?

A. Yes.

Q. And it was as a result of these discussions and references that you have referred to that this particular range was picked?

A. Right.

Q. And that seems to be the



range that is recognized at least by the community of which you are a member?

A. Correct.

Q. Is that a range specifically designed at the Hospital for Infants?

A. It is the general range applying to infants and children at our institution.

Q. Is there a difference between the general range for infants and children and the general range for adults?

A. We don't employ a difference.

There is a range for probably therapeutic

concentration of digoxin is the same in our

institution as it is in many adult institutions.

Q. We have had entered in evidence already and marked as Exhibit, I am not sure now, Exhibit 11, I don't recollect exhibit it was, but it was the reference to the Residents' Handbook.

MS. CRONK: Exhibit 16.

Q. Exhibit 16, Page 365 of the Handbook.

A. Yes.

Q. Now, as you see under reference values there is a reference, the optimal



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range	being	0.5	to	2.5	nanograms	per	milliliter
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Yes. Α.

All I want to ask you is this. Q. Do the figures that we see on Exhibit 15, the therapeutic drug monitoring program figures ---

> Α. Yes.

Do they represent a reduction in the hospital's view of what the therapeutic range is?

Α. They are somewhat a reduction, they were developed by different people. They were arrived at by different groups. I should point out something perhaps that you are not aware of, and that is that every patient report that emanates from the drug monitoring laboratory is a computerized cumulative report which has on it the therapeutic range of the drug that has been requested. So if a request has been made for digoxin analysis, the report will carry with the actual result the therapeutic range for digoxin at 0.8 to 2.0.

That is something that has Q. recently ---

That has been for at least Α. a year that we have been computerized, yes.



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Q. I just wanted to be clear
on this and I take it you are agreeing with me tha
between the time that this handbook was published,
the 6th edition in 1979 and 1982 or 1983, there
has been a downward change in the therapeutic
range that the Hospital recognizes.

THE COMMISSIONER: It is downward and upward, isn't it?

It is upward at the moment.

Q. It is upward at the bottom and downward at the top.

> Yes. Α.

THE COMMISSIONER: Thank you.

Q. It is revised upward at the bottom and downward at the top.

> A. Right.

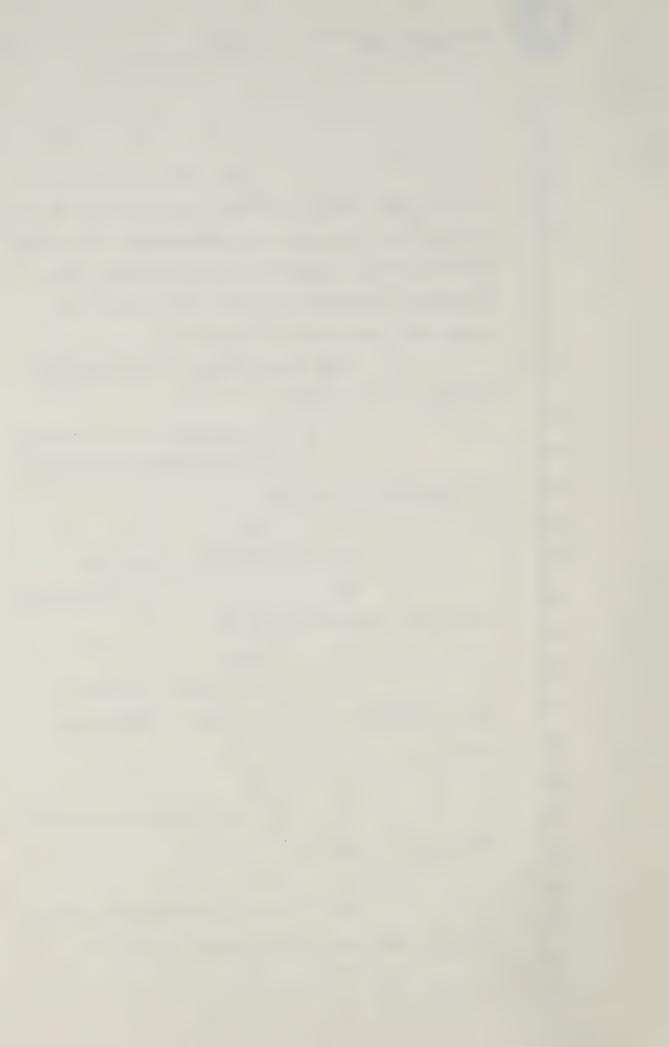
Now, Exhibit 15-B and C 0. also referred in the last column, "Interacting Drugs."

> Α. Yes.

Q. To the interaction between digoxin and quinadine.

> Α. Yes.

And I gather, again, looking Q. at your resume and without going through the



references themselves, that the interaction of various drugs is something with which you have had some both practical and academic experience.

A. Yes.

Q. In fact, you have written a paper and I think delivered a presentation -- I am sorry, written a paper on the interaction of digoxin with co-administered drugs.

A. Correct. I am one of the co-

Q. And you have also written another paper about the interaction of digoxin and verapermil.

A. Correct.

Q. And I would assume again that the cross reactivity between drugs is something that is very important to know about in a clinical setting.

A. Right.

Q. Not only so that you can know exactly what it is that you are analyzing, but also so that you can interpret the findings that you make so that you can treat the patient properly.

A. Yes.



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Q. Now, Dr. Ellis, I believe,
testified that in his view there were two types of
interaction, one which he called an analytical
interaction; and another which he called a
therapeutic interaction, do you recall his evidence

A. Yes, I think he explained it very well, yes.

Q. So I take it you agree with his characterization.

A. Yes.

Q. Which is quinidine, is it the kind that shows up analytically as digoxin or is it what I call the booster that boosts the digoxin level?

A. It boosts the digoxin level, it is not an analytical problem.

Q. So that in any particular infant receiving digoxin and quinidine at the same time is there a possibility that quinidine will have the effect of actually raising digoxin levels?

That is correct, yes.

If you have a steady state concentration of, let us say, one nanogram per milliliter of digoxin and then quinidine is added to the patient's drug regimen, you could anticipate that the digoxin



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concentration will increase.

Are you able to assist us 0. at all as to how much it would increase?

Α. I think they are variable, but it could double quite easily.

> Could it go higher than 0.

> > Possibly, yes. Α.

Q. Now, on Exhibit 24 which I think you still have in front of you, the TDX information, Page 17.4 of that.

> Yes. A.

0. That shows the interaction between digoxin, the assay, and various other drugs. In the very beginning of the left hand column it mentions digoxigenin 205%. I gather digoxigenin is one in the first category of interactivity that is the analytical interaction, is that it?

> A. Yes.

0. Do I read that correctly as saying that the assay would measure that particular compound and the results shown would be approximately double?

That is my understanding, yes.



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	Q.	Now, I	just wa	anted to	be sure
so that if	there is on	e nanogi	ram of d	digoxige	enin
per millili	ter in the	serum be	eing mea	sured i	it would
in fact sho	w up as two	nanogra	ams?		

It could show up as 2.05 nanograms per milliliter, it would show up as.

Q. Then at the top of the next column is a reference to digitoxin and, again, we have heard that digitoxin creates the same analytical problem.

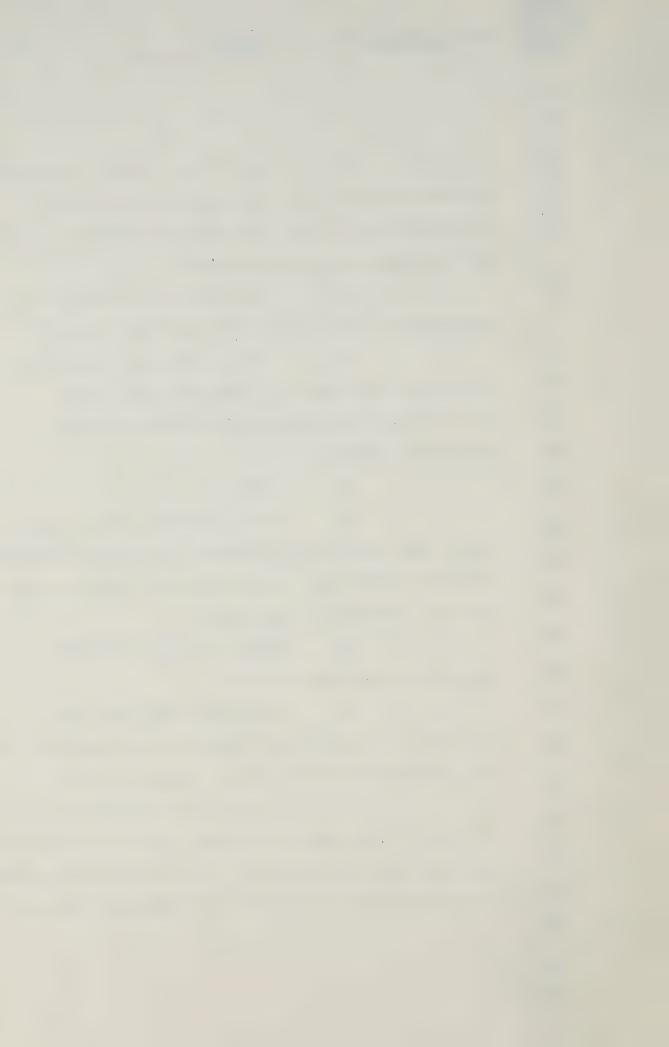
A. Yes.

But I had been led to under-0. stand that the effect of measuring digitoxin was that digitoxin would read on the assay at a higher basis than was actually in the serum.

A. Well, it has 3.6 crossreactivity, according to this.

Would that not mean that if you had 100 nanograms per milliliter of digitoxin in the serum you would only get a reading of 3.6?

A. I think the best interpretaion is given on the page before that, so if you would just go to the page before that, which defines the percent cross-reactivity is equal to 100 times the measured



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digoxin concentration divided by the concentration of the cross reactant. Now, all one has to do is put in the knowns and you can determine what the measured digoxin concentration would be for any of these compounds listed. You have a very simple equation there and the only unknown is the measured digoxin concentration.

Q. Yes.

And by applying that formula you will arrive at the cross-reactivity for the concentration of digoxin that -- that that particular compound would produce. For example, if we took progesterone because it is simple, because they are using figures of 10 milligrams per milliliter which has a cross-reactivity of .01 percent, and if we apply that formula, then it would be that .01 is equal to 100 times the measured digoxin concentration divided by the concentration of the cross reactant which in this case is 10 micrograms, or 10,000 nanograms. We have to convert to nanograms because we have to use the same units. If we did that little mathematical calculation it would work out that progesterone at a concentration of 10 micrograms per ml would read a digoxin concentration



of 1 nanogram per ml.

Q. So that the effect of all these things is that they will give a reading of digoxin in response to an actual concentration of the substance shown in the left hand column.

A. Yes.

Q. To a greater or lesser extent, according to the data that is supplied by the manufacturer.

A. Right.

Q. Given what you have told us about cross-reactivity, both your experience with it and the importance of it in a clinical setting, I take it that this sort of information is not only of significance to you but also exactly what you would expect to receive from a manufacturer of a particular assay.

A. It is what we would hope to receive, yes.

Q. It is pretty standard, I would think, in the industry.

A. It should be.

Q. Well, I asked Dr. Ellis last day about the problems at Antibodies Inc. and the



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fact that he had not been able to get information from them. I suggested to him that seemed incredible they couldn't provide that information. Does it strike you as incredible that the information isn't there?

- A. It is disappointing, yes.
- Q. Surprising?
- A. Surprising.
- Q. On Exhibit 24 at the

very beginning, the paragraph entitled "Intended Use" and about eight lines down, seven lines down, it says:

"Digoxin intoxication is a common and serious problem in the clinical setting."

And I believe you were here for Dr. Ellis' evidence when I asked him whether he was familiar with the literature in that regard. Are you familiar with literature to the effect that digoxin intoxication is a common problem?

- A. Yes.
- Q. Are you familiar with ranges suggested in the literature? I have seen references to anywhere from 10% to 30% of adult



patients being treated with digoxin.

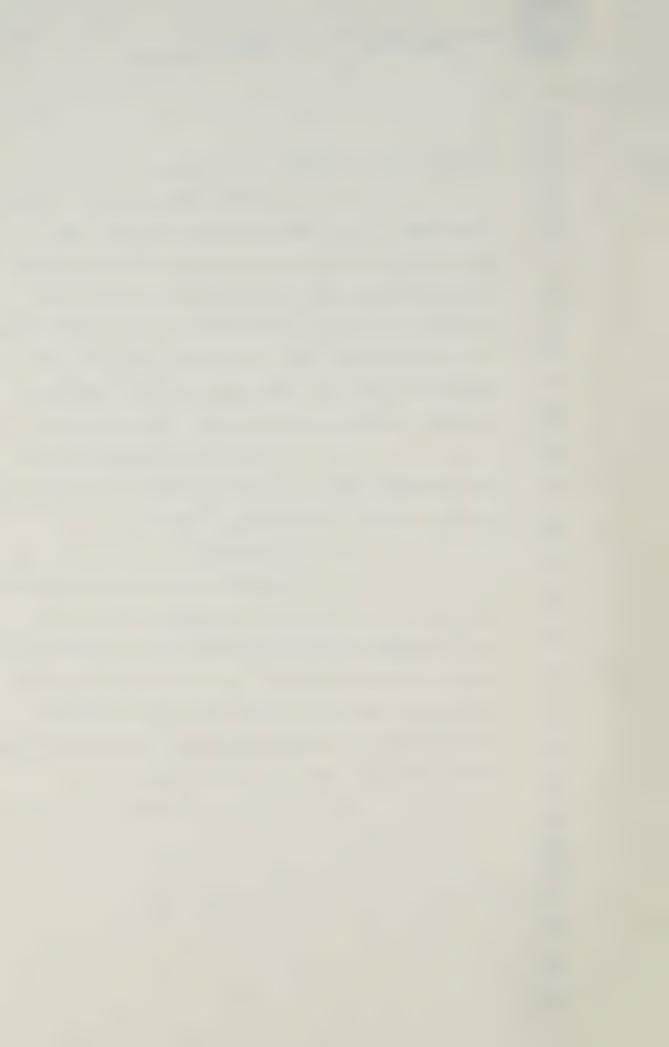
A. I think that is quite a high percentage in the ranges you are quoting. The diagnosis of digoxin toxicity is a clinical one as Dr. Ellis mentioned. The therapeutic monitoring laboratory would provide an indication that the drug concentrations are now approaching possible toxic concentrations. The Commission should, therefore, evaluate closely whether or not toxicity exists.

Q. Well, we know from what you have already said that your responsibility is not to do that clinical evaluation of toxicity.

A. Correct.

Q. But you can certainly speak for what you see in terms of the results you observe, and I am going to ask you, based on your observations at the Hospital for Sick Children, do they confirm that in the children being treated with digoxin, intoxication is a common phenomena, according to the levels that you consider to be toxic?

A. It occurs fairly frequently.



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				Q.	Can	you	give	us	any	assistance
as	to	what	the	degree	of	free	quency	y is	5?	

A. I think you will get a better percentage from a cardiologist.

Q. That is a fair statement, but I have a biochemist at the moment and I would appreciate knowing what you see in terms of your results?

A. But I don't see clinical toxicity; I see a digoxin concentration that may be over 2.

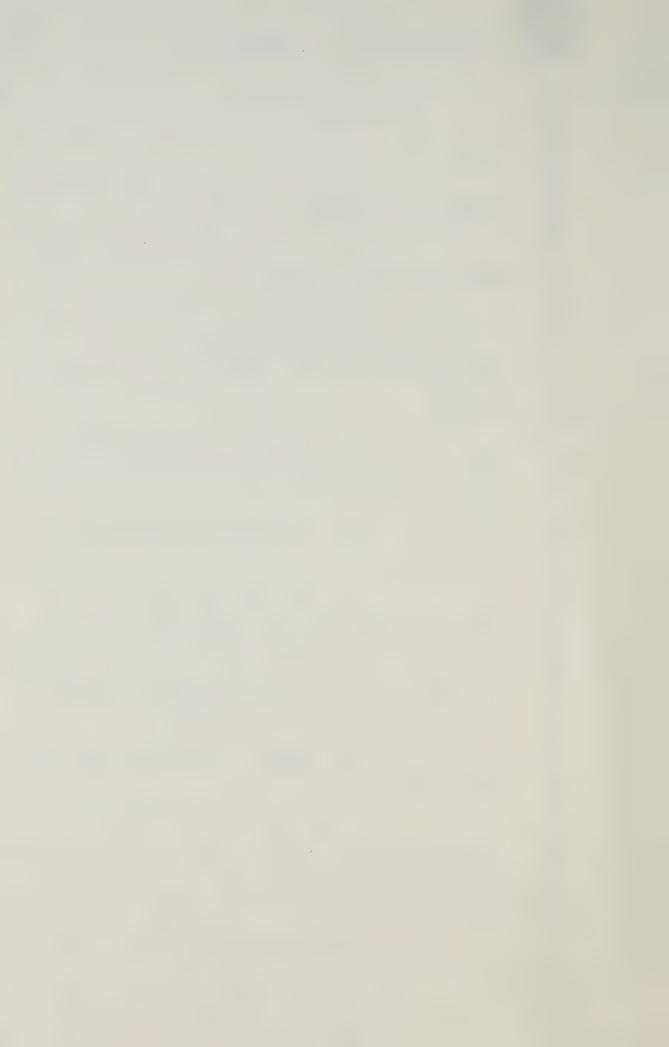
Q. That is what I am asking you about.

A. We can check that up. A significant number of the results that we measure are over 2. If you ask me for percentage, just without checking up, I would say somewhere between 10 per cent and 20 per cent probably.

MR. STRATHY: Thank you very much, that is fair.

I will undertake, Mr. Commissioner, for the witness at least, to refer him to the studies that I have mentioned as to the toxicity levels in adults.

THE COMMISSIONER: That is fine.



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MR. STRATHY: Q. If you could look at page 17.7, there is just one last matter on that exhibit that I would like to clarify. In the paragraph "Limitations of Procedure" --

A. Yes.

Q. It says, in the last sentence of the first paragraph, it says:

"Samples from patients receiving digitoxin or crude digitalis therapy will show falsely-elevated values for digoxin."

Now that is where I have trouble, because if you look at Table 1 which is the table of cross-reactivity, it does not suggest that digitoxin has such a high cross-reactivity, but I read the paragraph on 17.7 to say that if you use the test on digitoxin patients you will get values that are falsely elevated.

Can you help us with that?

A. That is a statement that they have made, and if you calculate from Table 1 on page 17.4 you can work out what the cross-reactivity would be, using the same formula we discussed. It would not be that much of an elevation, if you put these numbers into that formula.



Q. Whatever it is, it is clear I suppose that if you were to try to measure digitoxin you should not be using this assay?

A. No, the antibody is not for digitoxin, but it is for digoxin. Digitoxin cross-reacts to a small extent.

O. The most recent exhibit - or one of the most recent - was Exhibit 26, your slides. Looking at page 6, which is the second of two pages, you took us through the diagram on the left hand side and you mentioned an initial factor, patient compliance, that is whether the patient does or does not swallow his pill. Judging from your Form 15B and 15C that is a concern sometimes I suppose, particularly in children, that they do not take the pill that they have been given, or swallow the syrup, or what have you.

- A. It could be a concern, yes.
- Q. The next thing on that form is medication errors and I take it as given that medication errors are something that happen from time to time in hospitals. As long as there are human beings running hospitals there will be medication errors.

A. Right.



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that on	Ward	7F	ther	e wa	s a	medic	cati	lon	err	or	with
respect	to ep	oine	phri	ne a	nd '	Vitami	in I	E?			

- A. Yes.
- Q. Which resulted in sickness in a number of children?
 - A. Yes.
- Q. And I gather from what you are saying, from what you said in your evidence in chief, that with respect to the one child where there was a level of 1.3 digoxin, on Ward 7F, do you recall your evidence about that?
 - A. Right.
- Q. That there is at least a possibility, and I put no higher than a possibility, that there was a medication error in respect to that child.
- A. It is possible. That was the conclusion, I think, in the Dubin Report.
- Q. The other possibility, to paint the whole picture, is that it was substance X and not digo xin?
 - A. Right.
- Q. Do you, as a matter of your routine work at the Hospital, become involved in the



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analysis of samples in respect of which there have been medication errors?

- A. Occasionally, yes.
- Q. Is that something which you monitor, in a sense, medication errors?
- A. If one takes the 7F situation, these children became very ill. We did not know why they became ill. Because of the Hospital's history with digoxin we ended up doing a number of assays for digoxin.
- Q. That was after the recognition that there was or might be a problem. My question is, as a routine matter, are you watchdogs for medication errors?
- A. Certainly in the drug monitoring area, yes.
- Q. And drug monitoring in a sense of both before and since the Therapeutic Drug Monitoring Program?
 - A. Yes.
- Q. And you are using drug monitoring not as a label for the particular program that you have introduced recently but for the process that you are engaged in and have been engaged in while you have been at the Hospital?
 - A. Yes.



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Q. When a medication error takes place, is there some sort of a report that is prepared?

A. You would have to ask the clinicians running the wards. We would report everything that our laboratory does. It is then in collaboration with the clinicians. In the 7F situation, the infants became very ill and a lot of additional tests were done, not just digoxin.

Q. Let me be more specific. In your between monitoring, if you detect something which appears to reflect a medication error, does your laboratory prepare some sort of a report?

A. No report other than the normal report. What we would do is relay our findings. Let us say a patient was given an inadvertent amount of another drug, let us say, theophylline or phenytoin, we then measured the concentration of this drug, found it to be extremely high, so the clinicians on the ward as well as the clinical pharmacology unit as well as - well, these two areas would be contacted immediately. In fact, it is routine practice whenever we have a concentration over a particular level, over a particular value, to immediately phone the ward as well the



clinical pharmacology division.

Q. Let me just try and hone down my question a little.

First of all, I gather there would be several potential types of medication errors.

You might have, firstly, a child given too much of a drug which had been prescribed for him or her. That is one type of error that could happen, is it not?

- A. Yes.
- Q. If you are monitoring that drug that would be something that would hopefully show up in your monitoring?
 - A. Yes.
- Q. You would detect higher concentrations than should be there?
 - A. Yes.
 - Q. And you would report that to

the ward?

- A. Immediately, and to the clinical pharmacology division.
- Another type of error that could happen is that a child could be given a drug that was not prescribed at all for him, or her?
 - A. Right.



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			Q.	Is	that	something	that	would
be	detected	in	your	moni	itorin	ng?		

That is almost impossible to track down. It is very difficult, as the 7F situation showed. Children were given a drug which was not prescribed. It took many weeks to track that down.

Q. So in the clinical monitoring that you do, you are only monitoring things that are expected to be found in the child?

> Α. Yes.

Q. Let me ask you this. When you do detect that there are excessive concentrations of a drug that has been prescribed for the child, you say that you notify the ward and you notify the clinical ---

> Pharmacology Division, yes. A.

0. Do you do that - is there any report that you do to them or ---

Well, there is immediate A. notification by telephone that the results are abnormally high in such and such a patient for such and such a drug.

Apart from that, there is the usual reporting system which is that at 1600 hours every day

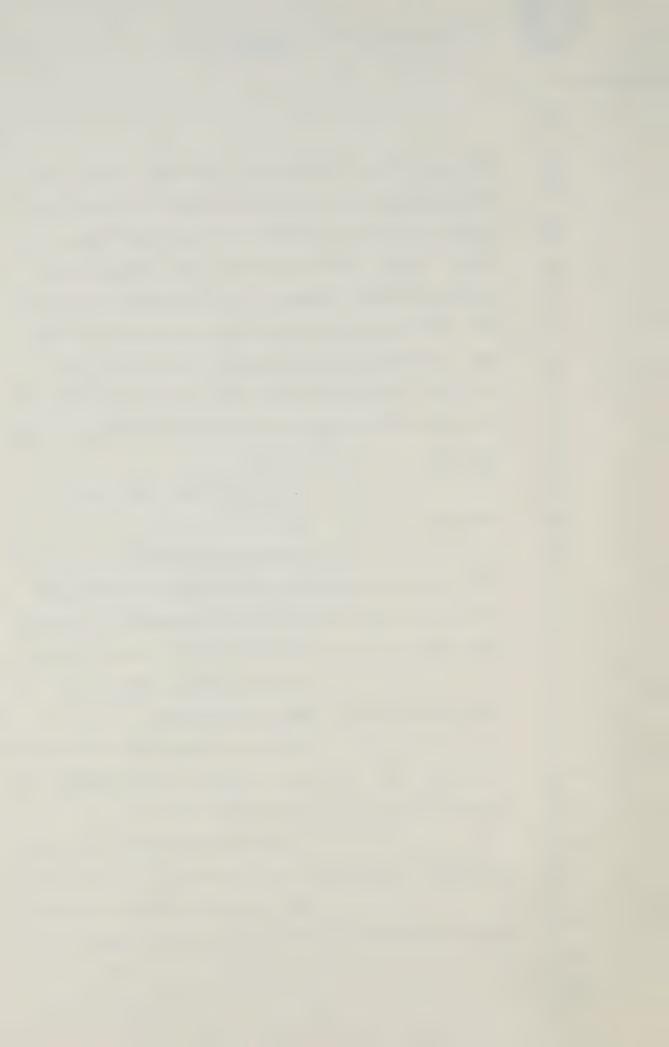


the results are reported to the wards on all the analyses which we perform. At 1600 hours we also print out what is known as an Exception Limit Report Form. This Exception Limit Report Form reports all the concentrations measured during that day which were very sub-therapeutic or toxic, and a copy of that computer printout is given to the Clinical Pharmacology Service at 1600 hours as well as to the Microbiology Service and Infectious Disease Service.

 Ω . Let me ask you one final question.

In your experience prior to March of 1981, in the therapeutic monitoring of digoxin, had you encountered instances which appeared to reflect medication errors in the administration of digoxin?

- A. Prior to March 1981 I was not responsible for digoxin analyses.
- Q. That is probably the best answer you could have given me. Are you able to assist us in that at all? I suppose you cannot?
- A. I was not responsible for it, unless Dr. Ellis would have brought it to my attention.
- Q. How long is it that you have been responsible now for digoxin monitoring?



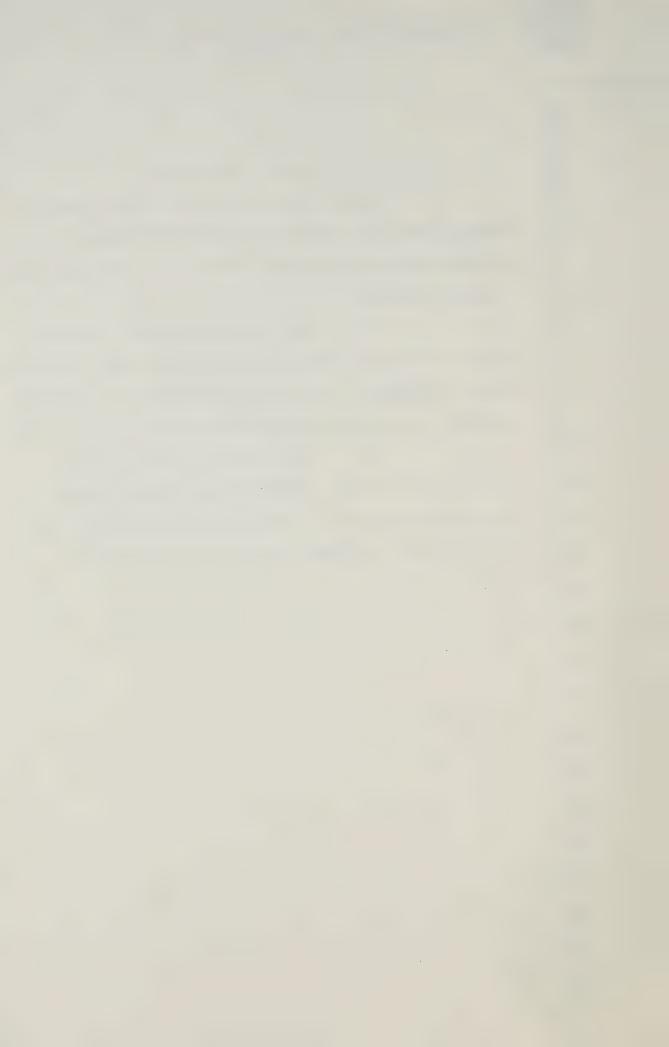
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A. Since July of 1981

Let me ask you, in that period, Doctor, had there been instances which appear to reflect medication errors or errors in the administration of digoxin?

Not to my knowledge. There is Α. no doubt we get children that develop toxic concentrations of digoxin. They need alterations in the drug regimen. It is not a medication error.

Q. Can you go as far as to say this, that you have observed toxic levels which you cannot necessarily say why they are toxic? All it is is that you have observed toxic levels.





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A. One observes toxic levels
because of the individual difference in drug
disposition. As I explained yesterday, you cannot
predict a serum concentration for any given dose. So
you've got to try a dose, a recommended dose and
then you have to follow that up by measuring the
serum concentration.

Q. Well, have you observed levels in that time period that you've mentioned since you started doing it, that were sufficiently high that they might reflect the medication error?

A. We've observed levels. I think the highest level we have observed in the routine monitoring is probably around 14.

Q. 14?

A. 14 nanograms per millilitre.

Q. And is that a level that ---

A. Well, that child actually got into some digoxin tablets of its parents. So, it was a toxic overdose situation.

Q. That's not therapeutic monitoring?

A. No, but we were involved. We have observed levels between 5 and 10 occasionally; not too frequently but occasionally. The decision



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as to whether that is due to a medication error, I would advise you to ask Dr. Speilberg and Dr. MacLeod, the Clinical Pharmacology people.

Q. All right. So that is really not something that you are able to comment on?

A. No.

Q. All right, thank you, Doctor. Those are my questions.

THE COMMISSIONER: I think we'll probably rise now but I might get some indication as to timing. Mr. Hunt, have you any thoughts on how long you will be?

MR. HUNT: 15 minutes.

THE COMMISSIONER: You are next, Mr.

Shinehoft?

questions.

MR. SHINEHOFT: I don't have any

THE COMMISSIONER: Ms. Jackman?

MS. JACKMAN: Unless my questions are asked, I only have about five minutes.

THE COMMISSIONER: Five minutes.

Miss Kitely?

MS. KITELY: 10 or 15 minutes at the outside, Mr. Chairman.

THE COMMISSIONER: Mr. Young?





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MR. YOUNG: I have no questions,

Mr. Commissioner.

THE COMMISSIONER: Mr. Ortved?

MR. ORTVED: I have no questions at

the moment.

THE COMMISSIONER: Mr. Olah?

MR. OLAH: Well ---

THE COMMISSIONER: No, I'm not, I just

want to know how long you will be?

MR. OLAH: Mr. Commissioner, the problem I've got, as you may have seen, I was away for part of the morning and I would like to verify that some of the questions I have have not already been asked, so, I can't be precise. But certainly I will be short.

THE COMMISSIONER: All right.

Mr. Tobias?

MR. TOBIAS: 15 minutes, Mr. Commissioner.

THE COMMISSIONER: Mr. Labow?

MR. LABOW: No questions at the moment,

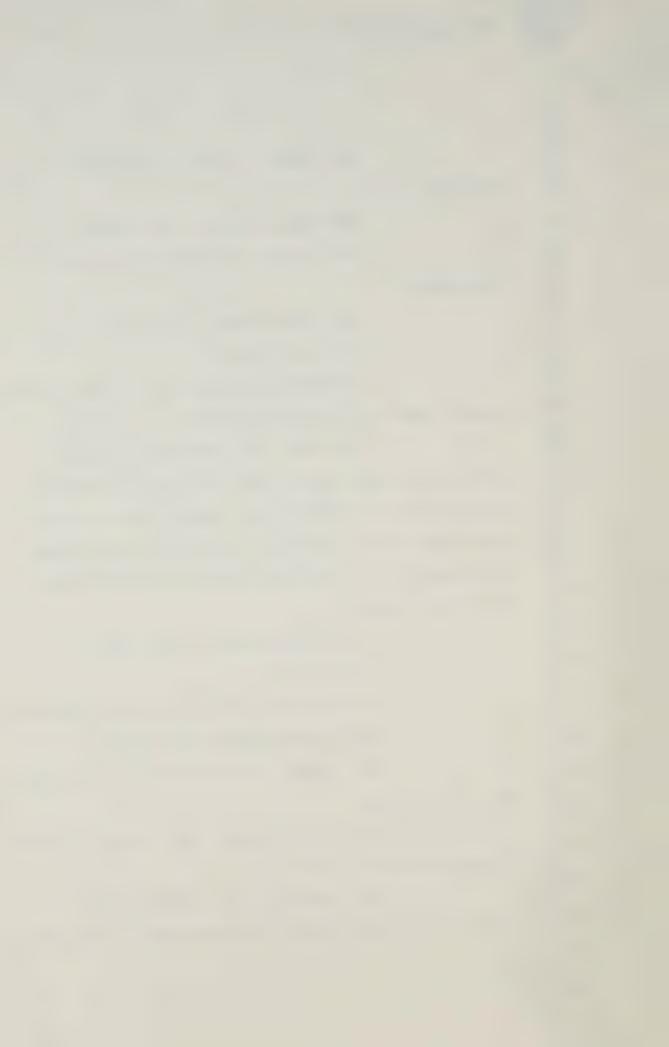
Mr. Commissioner.

THE COMMISSIONER: Mr. Roland? I take

it you want to be last?

MR. ROLAND: Yes, I would like to be

last and I do have one or two questions at the moment



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and I may have more, depending on other questions asked. Thank you.

THE COMMISSIONER: Well, that - you may have some re-examination in any event.

MS. CRONK: Yes, I anticipate some questions.

THE COMMISSIONER: Well, I don't think there is any need to make any special arrangements. I think we will just carry on until one o'clock and see what the situation is then, but it does not look as though we will certainly not get to another witness that we can complete.

MS. CRONK: Thank you.

THE COMMISSIONER: Yes, all right.

Oh, sir, where is Miss. Solomon?

MS. SOLOMON: Here.

THE COMMISSIONER: Oh, yes, sorry, I

missed you. Did you have any questions?

MS. SOLOMON: I have no questions.

THE COMMISSIONER: No, all right,

thank you.

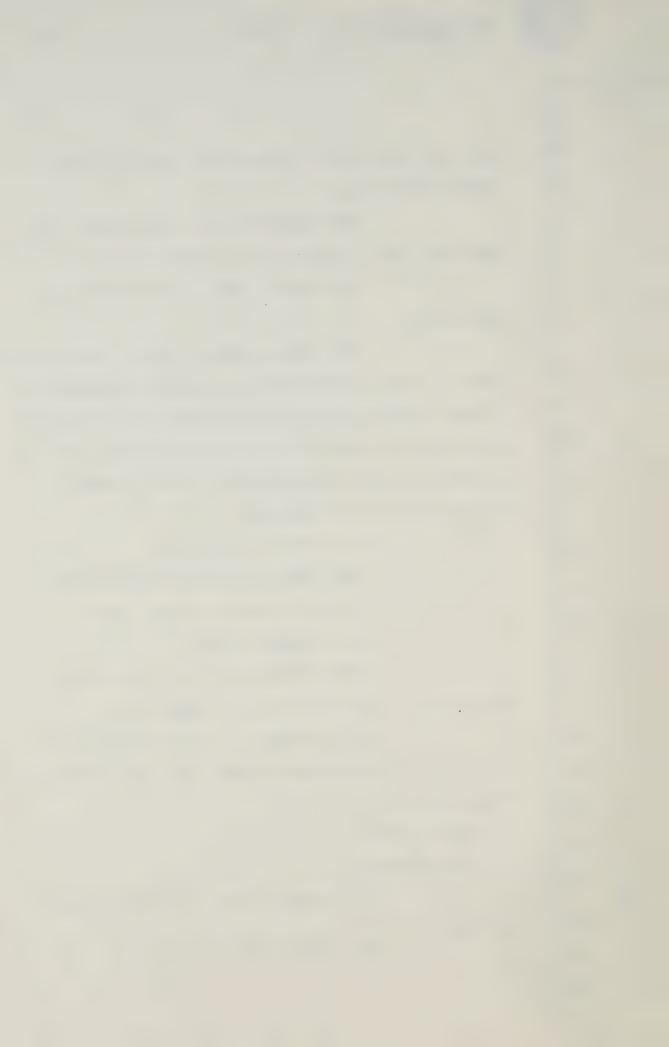
--- Short recess

--- Upon resuming:

THE COMMISSIONER: We'll try again,

Mr. Hunt.

MR. HUNT: Thank you, sir.



CROSS-EXAMINATION BY MR. HUNT:

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Q. Dr. Soldin, with respect to the FPIA method, I take it that you have given really two guarded conclusions at this point in your experience with it; that is, one, that it is more specific than RIA and, two, that it gives generally lower readings than the RIA method?

A. Lower readings in patients not on digoxin, not known to be on digoxin. Those are guarded conclusions, yes.

Q. And with respect to the post mortem samples.

THE COMMISSIONER: I am sorry, I didn't get the answer. Did you agree with that leading question, that it is more specific and it is lower than RIA?

THE WITNESS: I'm saying it could be more specific, yes. Our findings at the present time would indicate that it probably is.

THE COMMISSIONER: And what about being

lower?

findings are on the average in patients that are not receiving digoxin, that is, we have done some studies on the neonates not on digoxin, as well as on the



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autopsy samples, in those two areas.

MS. CRONK: Excuse me, Mr. Commissioner,
I too am having difficulty hearing the witness.

THE WITNESS: I'm sorry, in those two areas the results by FPIA tend to be lower than the results by RIA.

MR. HUNT: Q. So, with respect to the post mortem samples that were analyzed, am I correct that in 23 of the 36 cases, the results were negative, that is, they were lower than .5.

A. In 23, yes, they were lower than .5 in what I would call Group 1, 23 of that.

Q. All right. And that in nine cases the RIA analysis gave a reading that was higher than the FPIA analysis?

A. That's correct.

Q. And in two cases ---

A. That would be Group 3.

Q. All right. We're still dealing with the 36 post mortem samples?

A. 37.

Q. 37, all right. In two cases the FPIA analysis gave a higher reading than the RIA?

A. Group 4, yes.

Q. All right. Now, my point is this,



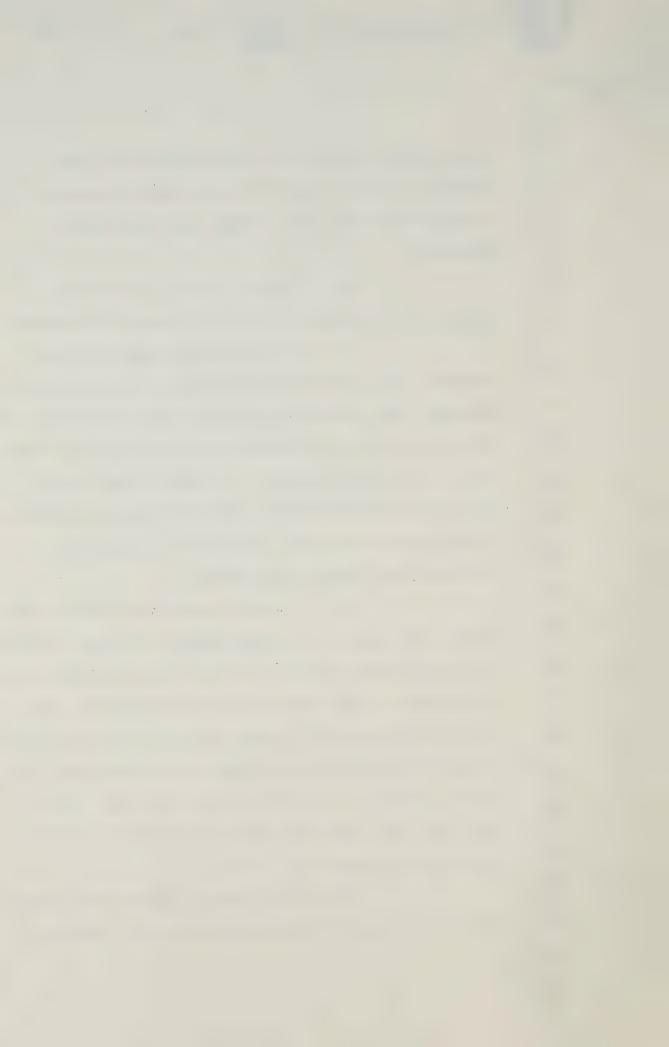
is it valid to draw any conclusion at all with respect to the analysis of post mortem samples in light of the very small number that have been analyzed?

A. Well, I think I have been sufficiently guarded in my conclusions this morning.

Q. Well, you have said you were guarded, sir, but you have also said that you would conclude that probably the FPIA is more specific. It's the use of the word "probably" at this point in time that I'm concerned with. In light of the small number of instances where there has been an analysis of post mortem samples, is it fair to draw any conclusion at all at this stage?

number and then it's an individual's decision on the way he views the situation. So, I can only give you my decision. Your decision may be different. My view of the material is that there are, out of these 37 patients, there are in fact 12 patients that had results lower by the FPIA than by the RIA. There were only two that had results higher by the FPIA. So, the ratio there is 12 to 2.

Then if we look at the neonatal study in which five patients had their digoxin, apparent



digoxin concentrations measured by both technologies
all five were well, I'm sorry, I stand correct on
that. In two of the five, the results essentially
were the same, and in three of the five the results
by FPIA were lower than the RIA results and in none
of the five was the reverse true.

Q. Well, in the case of post mortem samples, the reverse was true in two cases?

A. In two out of 14 cases.

Q. But my point is, the very fact that you are coming up in such a small number of samples with different conclusions, does that not really leave us in a state that at this point it is just not valid to be drawing any conclusions at all?

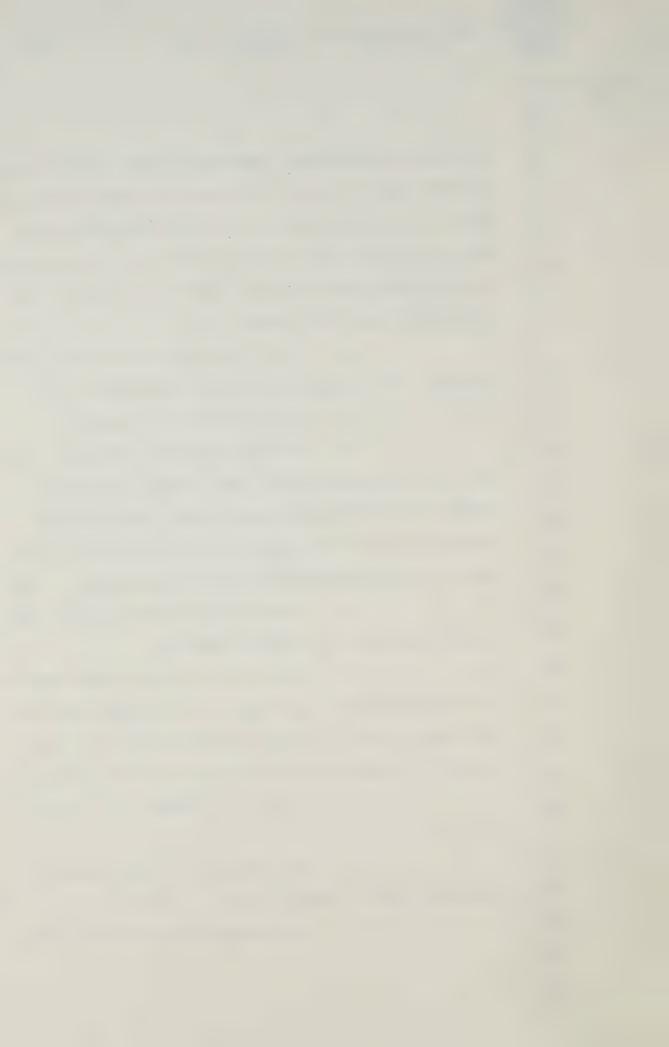
A. That's your reading of the data and my reading is a little different.

Q So, to be clear, on your reading you are prepared to say that it is probable that the FPIA will give - it is more specific and will give a lower reading in cases of patients not on digoxin?

A. With the evidence in front of me, yes.

Q. Notwithstanding the number of cases that we're dealing with?

A. Altogether we have 15 in which



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the FPIA is lower than the RIA and we have two in which the reverse is true.

Well, I put it to you, you will 0. be a lot more comfortable with your conclusion, whatever it is, once hundreds of these have been done?

> That's correct. A.

Q. And once hundreds have been done, I put it to you that you would be prepared to change your conclusion if that was warranted?

> A. Certainly.

Now, if I could just ask you Q. about the reference in Exhibit 25 on the last page to the HPLC analysis that was done. Perhaps I could show you my copy.

The only question I have with respect to this is that that would appear there was only one lab that reported on that particular type of test?

> With HPLC? A.

Q. Yes.

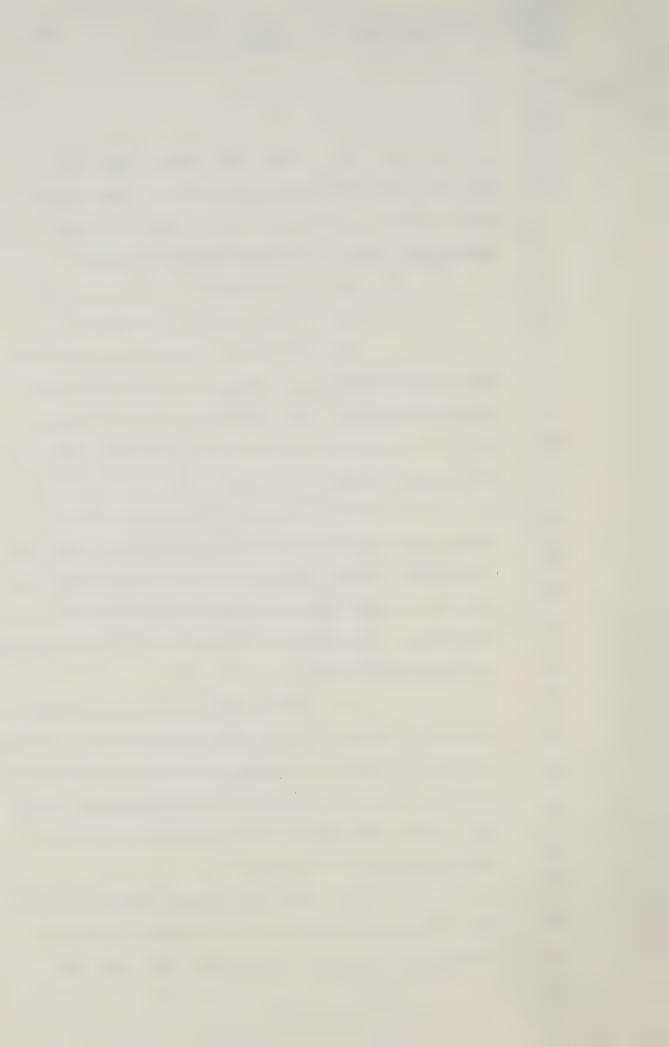
Yes, correct. A.

And in light of the fact that Q. there was only one lab that reported on it, really, again, would it not be fair that it is impossible to draw any conclusions with respect to the accuracy or inaccuracy of that method as used by that lab?



		A.	Well,	as	used	by	that	lab	one
can	certainly	draw s	ome con	clu	sions	S .	The	resul	Lts
were	abysmal	by that	lab.	So,	I th	nink	on	that	
part	icular sa	mple, t	hat lab	pe	rform	ned	poor	ly.	

- Q. All right.
- A. If I could -- I'm sorry.
- Q. I'm sorry, maybe this will be what you're coming to. Before you could take the conclusions beyond that particular lab, you would have to know much more about the technique used and the detector used?
- A. Correct. One could draw conclusions only to that lab, the lab that used that technique. I have, as I have expressed already, my own reservations about the use of HPLC for the measurement of digoxin concentrations in a therapeutic drug monitoring scene.
- Q. Now, with respect to Substance X and HPLC, we can all agree that Substance X is unknown and that it could be similar to digoxin in structure, and if it is similar to digoxin in structure, would that be the worst case from an analytical point of view in trying to identify it?
- A. Yes, the more similar it is the more difficult it will be to separate it chromatographically. Now, as I have explained, one can



achieve identification notwithstanding this fact through the use of a mass spectrometer.

Q. All right. There are other compounds which are similar to digoxin, I understand, such as, digitoxin and dihydrodigitoxin and dihydrodigoxin?

A. Yes.

Q. And would you agree with me that those compounds can be separated from digoxin by HPLC?

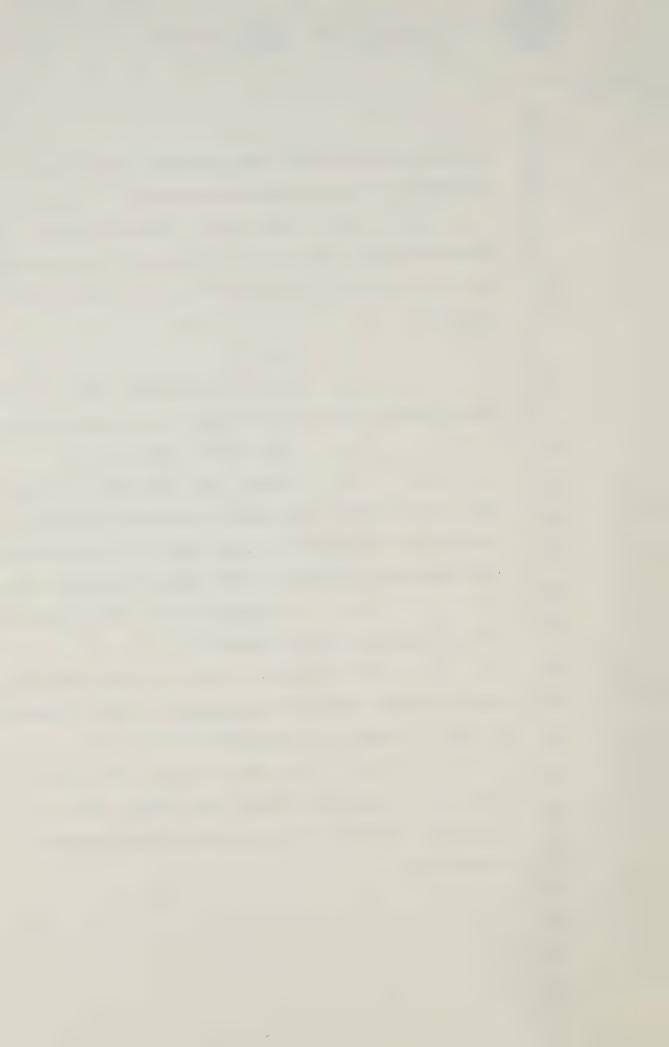
A. Yes, that's true.

Q. And the fact that HPLC has been able to separarte other similar compounds from digoxin, would it not suggest that that method is one that may well separate Substance X from digoxin when it's tried?

A. It suggests that, but it doesn't prove it, and one has to prove it.

Q. Right. And if my understanding, which is very limited with respect to HPLC is correct, it uses a column as a separation device?

A. It uses a column and a mobile phase as a separation device. The mobile phase is a critical component of any liquid chromatographic separation.



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Q. But am I correct that there are different types of columns that can be used along with the other phase?

A. There are, yes, there are a large number of columns.

Q. And just the two that I have heard about are the reverse phase column and the absorption phase?

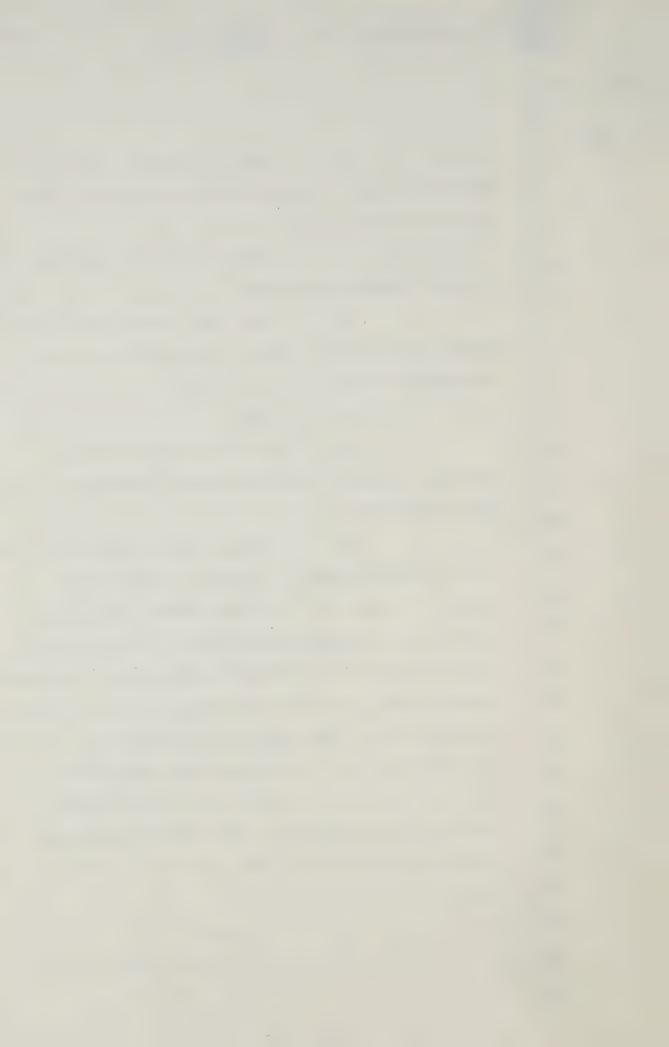
A. Yes.

Q. Is it true that these different types of columns separate compounds in different ways?

A. Separation is achieved, it can be in different ways, it depends on what your mobile phase is. If, for example, you add a iron into the mobile phase, then you will in fact be creating an iron exchange column out of the reverse phase column, so that your technique for separation becomes one of iron exchange chromatography. So there are different ways of causing these separations.

Q. So if you used different columns, you can separate the different compounds in different ways, or the same compound in different ways.

- A. You could.
- Q. Now, if HPLC has been used to



separate compounds which are similar to digoxin,
and there are different ways of using HPLC to
separate compounds in different ways: if two
different columns separate a compound does that
not suggest that that particular approach is
likely to be one that provides some greater degree
of accuracy in terms of ensuring that one has
separated the compounds?

- A. Yes, I agree with you it increases the chances that we might be able to separate or be able to tell whether we have separated digoxin from substance X. It may not be able to prove it, though.
- Q. Would you agree that it would be unlikely that substance X and digoxin would come off the two different columns at the same time?
 - A. They may.
- Q. They may, but how likely do you think that would be?
 - A. I think it is probably unlikely.
 - Q. Now, with respect to Mr.

Cimbura, you sat through his evidence?

- A. Some of his evidence.
- Q. You were not here for all of it?



A. No.

this point in time, I am asking you if this is a fair statement of your position with respect to him. Would it be fair to say at this point in time that in terms of you giving any opinion on his method and the accuracy or inaccuracy of it, that in the evidence that he has given so far you did not get the data required to allow you to give such an opinion?

A. I think that is true in an overall sense, some data was given which I could comment on.

questions about some of the procedures that he used based on some of the data that was given.

Or that you would at least like to know more about certain aspects of it. In terms of being able to give an opinion on the accuracy or inaccuracy of the results of his investigation at this point in time, is it not fair that you do not have all the information you would need to have?

A. No, I think that is inappropriate. In other words, I feel that there are
aspects that I would be as a scientist critical of at



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this point in time. There are aspects that I wouldn't want to address at this point in time because I don't have the data, as you pointed out.

Q. Well, I assume as long as there is one aspect that you don't have the data with respect to, that in terms of giving an overall opinion you would want that data before you ventured such an opinion.

A. I don't think that is necessary at this point in time.

Q. What is it that you don't think is necessary?

A. To get all the data. I think it is important to get the data to have a critical look at the entire methodology, aspects have been mentioned which I personally am not happy with.

Q. At this point in time when we are dealing at this phase of these hearings with methodology, there is data that you do not have from Mr. Cimbura that you would need in order to give that type of an opinion on his methodology.

A. To evaluate the entire method, yes.

MR. HUNT: Those are all my questions.

I have. Thank you, Mr. Commissioner.



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Rosenberg.

THE COMMISSIONER: Thank you. Mr.

MR. ROSENBERG: No questions.

THE COMMISSIONER: Mr. Shinehoft.

MR. SHINEHOFT: I have no questions,

Mr. Commissioner.

THE COMMISSIONER: Miss Jackman?

MS. JACKMAN: I was going to wait

until after Miss Kitely.

THE COMMISSIONER: You were going

to wait until what?

MS. JACKMAN: Miss Kitely and I agreed that she go first.

THE COMMISSIONER: Oh, I see. All right, Miss Kitely.

MS. KITELY: Thank you, Mr. Commissioner.

THE COMMISSIONER: The only problem is

I might forget you.

CROSS-EXAMINATION BY MS. KITELY:

Q. Dr. Soldin, I am assuming since the slide projector is still here that we didn't see all the slides yesterday, do you still have a couple left?

A. Yes.

Q. Could you go through them for

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us?

A. Yes.

THE COMMISSIONER: That is exactly the kind of question I would hope you would have got rid of at the session yesterday. You don't have any idea what is in them, you have no idea whether they will help us or not.

MS. KITELY: Yes, I do know what is in them, sir, and I think they will be helpful. I thought it easier for Dr. Soldin to give the explanation than me to try to drag it out of him.

THE COMMISSIONER: You did go through them with him?

MS. KITELY: I went through it with him at the break.

THE COMMISSIONER: Yes, all right.

THE WITNESS: I will be very brief.

The slides pertain to the appropriate sampling time for digoxin analysis.

THE COMMISSIONER: I'm sorry, they pertain to the appropriate what?

THE WITNESS: Sampling time.

This slide shows the time that it takes for digoxin to distribute between the tissues and plasma after the administration of an IV dose of



Soldin cr.ex. (Kitely)

the drug. As you can see, it takes approximately six hours for equilibreation between plasma and tissue, and it is for that reason that sample should not be drawn prior to six hours for the measurement of digoxin. The ideal sampling time in a therapeutic drug monitoring laboratory for really all drugs, there are one or two exceptions, should be, the sample should be drawn just before the next dose of the drug.

Now, if digoxin is administered every twelve hours the sample should be drawn just before the next administration. If digoxin is given orally instead of intravenously, it also takes approximately six hours for that equilibreation.

What I wanted to convey with this slide is that when a drug is administered at intervals equal to its half life, it takes approximately five half lives to reach a steady state plateau. What we have here is an increasing curve, that is, the concentration of digoxin is increasing with time as the digoxin administration continues and the important parameters here are that the steady state concentration, that is, where we have a plateau, the steady state concentration for most drugs is directly related to the drug dose.



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So if you double the drug dose, then you tend to double the steady state concentration, and if you halve the drug dose, then you would halve the steady state concentration.

Now, there are exceptions to that So the optimal sampling time, therefore, rule again. should be at steady state. One should wait until the patient is at steady state, which means one should wait five half lives after the commencement of therapy, unless one uses a digitalizing dose or a higher dose to start the therapy, in which case one could start monitoring earlier.

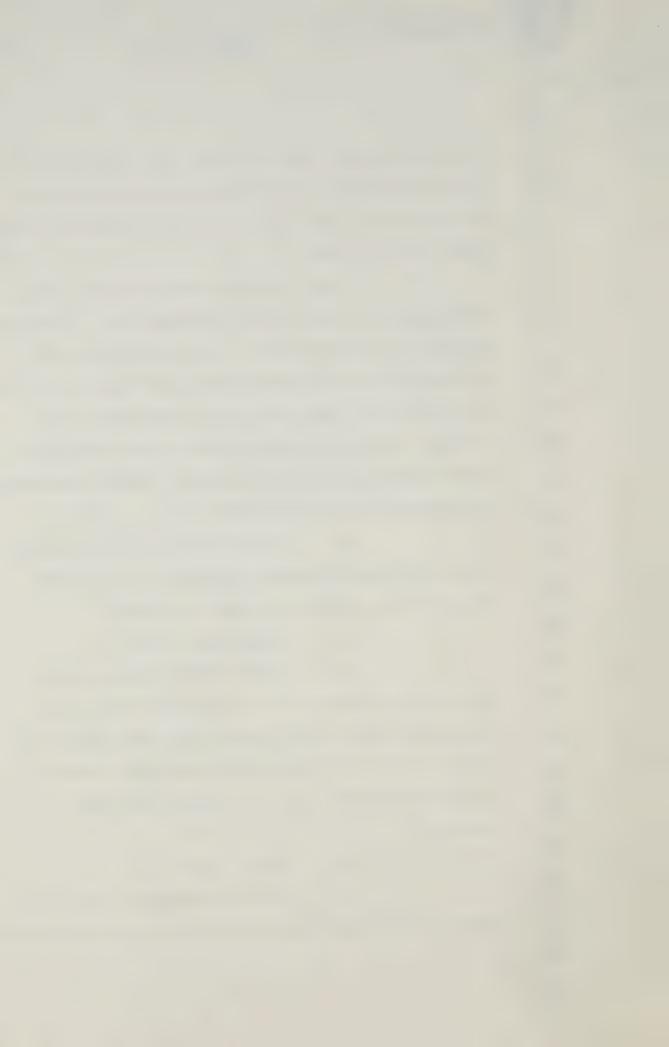
0. Just as the copies of your slides were made available yesterday, Dr. Soldin, might we have copies of those two slides?

Certainly, yes.

Q. Now, Doctor, when Dr. Ellis was on the witness stand he was asked about the multiplier effect and that was as between serum and tissue on the one hand and pre and post mortem on the other hand. Were you present for that evidence?

> A. Yes, I was.

And he produced a couple of articles which have been made Exhibits 19 and 20 after



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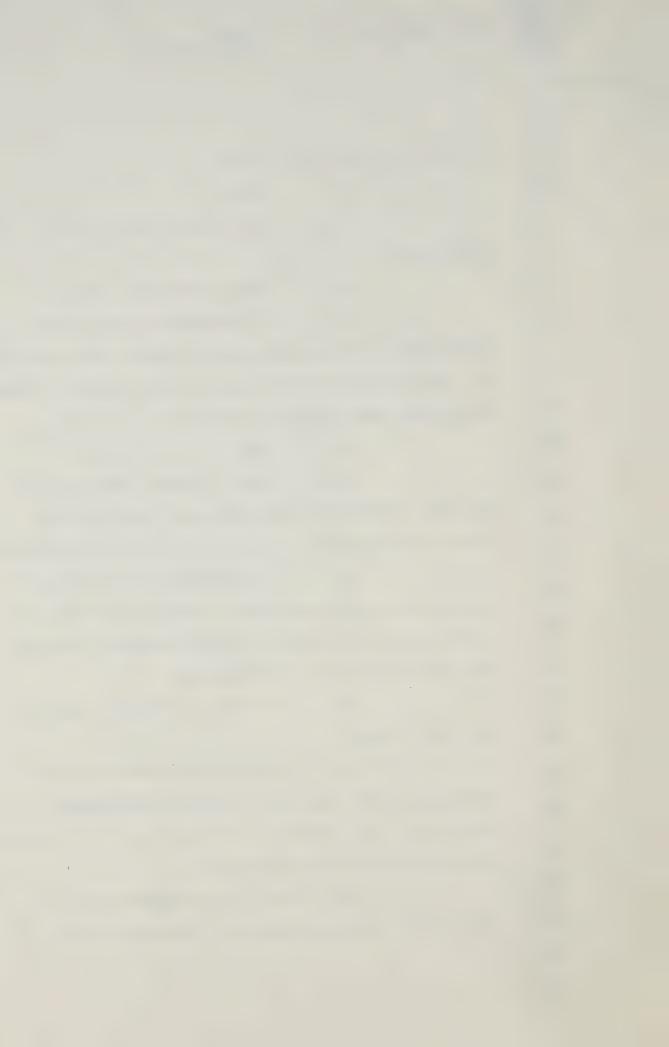
he got off the witness stand.

- A. Yes.
- Q. And you have seen those

articles?

- A. Yes, I have seen them.
- Q. I indicated to you in the break that I intended to ask you about those because Dr. Ellis said you could help us with further information about the multiplier effect.
 - A. Yes.
- O. And I gather that you are not very comfortable with that and that you feel there is someone who is more able to answer questions.
- A. I think that the best person to ask about that particular effect, or a very good person to ask would be Dr. Steve Speilberg from our division of clinical pharmacology.
- Q. Why do you think he would be the best person?
- A. Well, he has done a lot of reading in that area and I have had discussions with him on it. So I think you will get up to the minute data from him of his evaluation.

MS. KITELY: Mr. Commissioner, we asked last evening whether Dr. Spielberg would



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for you.

be called and I don't know that we got a positive reaction, but I will certainly waive any questions of this witness if Dr. Speilberg is coming.

THE COMMISSIONER: I don't want to make too many rash promises because sometimes we put a witness in for one question and he stays a week.

MR. LAMEK: Mr. Commissioner, it is our expectation that Dr. Speilberg will be called as a witness but he's not available at the moment.

MS. KITELY: On that understanding I will leave the topic, sir.

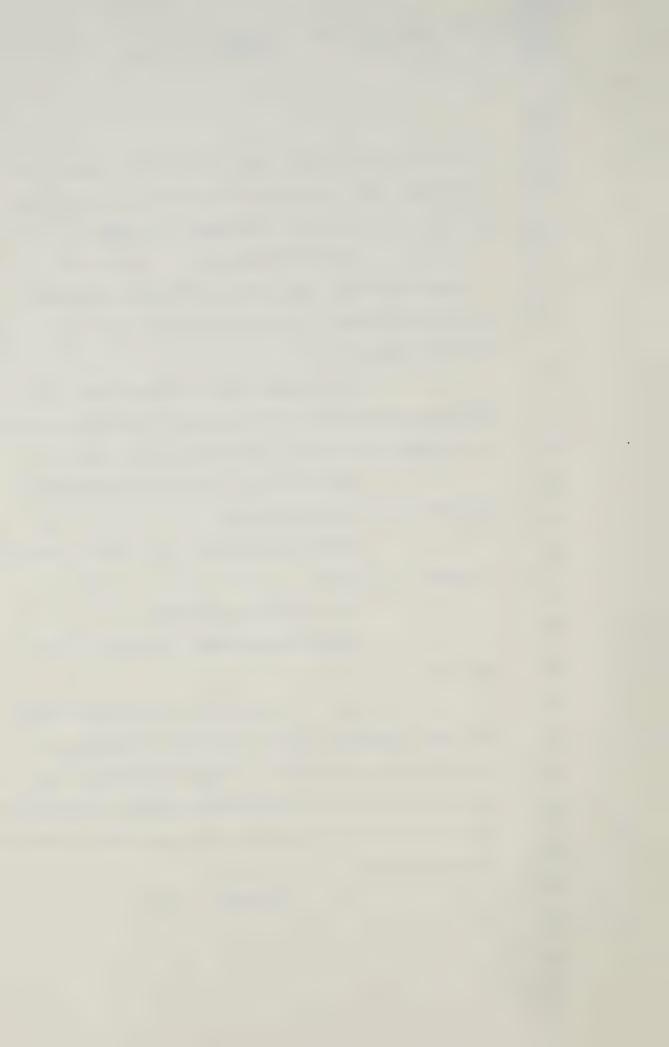
THE COMMISSIONER: It is not exactly a promise in blood.

MS. KITELY: In serum.

THE COMMISSIONER: In serum, good

Q. Well, Mr. Strathy was asking you some questions about the effect of some other drugs such as quinidine. I note included in the documents that were placed on the table this morning was, I guess it is called an abstract from a magazine, is that correct?

A. Correct.



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	Q.	Now I	und	lerst	tand	you	to	be	the
author of an	n article	about	"In	tera	actio	n of	D	igox	in
with Co-adm:	inistered	Drugs		Is t	that	corr	rect	t?	

Yes, I am one of the co-authors.

What we have is an abstract, not the entire article, obviously.

> Yes. A.

From what magazine is this

abstracted?

As it states "Clinical and A. Investigative Medicine".

Would the article be available?

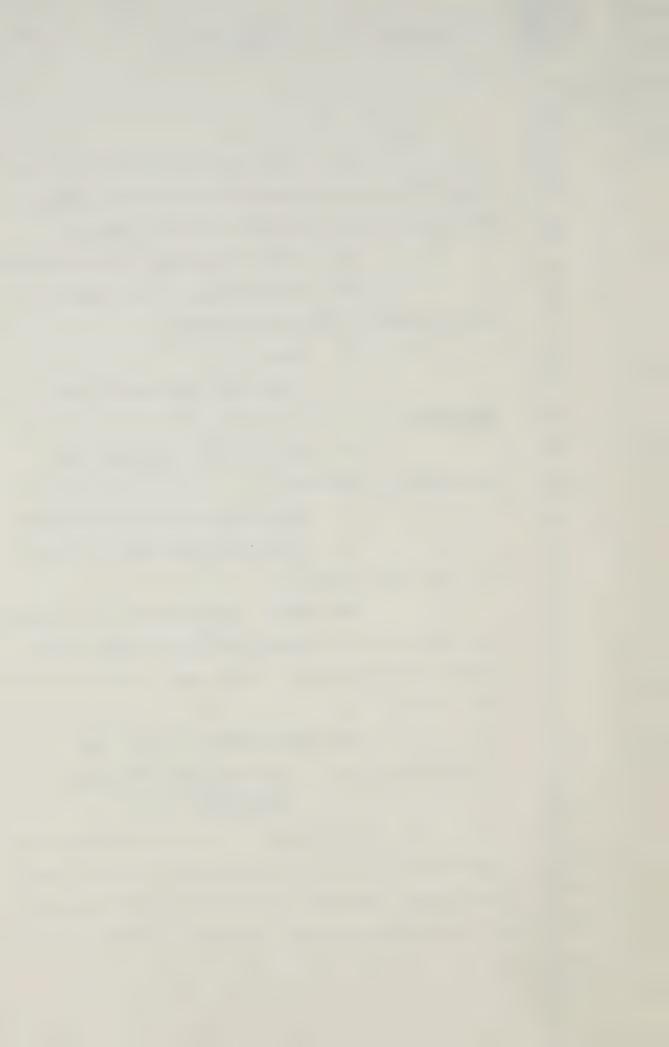
I am sure you could get that or I could get it for you.

MS. KITELY: Dealing with the abstract, Mr. Commissioner, I wonder until we get the actual article, if the abstract itself might be marked as the next exhibit?

THE COMMISSIONER: Exhibit 28.

--- EXHIBIT NO. 28: Abstract from "Clinical and Investigative Medicine".

MS. KITELY: Q. Now from reading just the abstract I gather that you looked at four drugs specifically and they would appear at the beginning of the article quinidine, verapamil, amiodarone and --





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A.	Indome	thacin
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Q. Yes, thank you. The results are different, as I understand it, and if I can take you to the first sentence in the Abstract itself and the third sentence?

A. Yes.

Q. Namely that quinidine, verapamil and amiodarone have a tendency to show elevation whereas the other drug tends to show a decrease - has that simplified it?

A. No.

Q. Is that an accurate reflection of the conclusions that you drew?

A. No, you have got it wrong. The three drugs have been shown, quinidine, verapamil and amiodarone, have been shown to have a effect on digoxin clearance by the kidney and through that effect they cause or can cause an elevation in the serum or plasma digoxin concentration.

Q. They can cause what?

A. An elevation, an increase.

Q As much as double, is that what you said earlier?

A. Well, approximately.

Now, the other drug, indomethacin, works differently. Essentially it decreases the



GFR which is the Glomerular Filtration Rate and as a result of a decreased GFR digoxin is removed also to a lesser extent and therefore this leads again to an increase in digoxin serum concentration.

Q. So they all - the administration of all those four drugs can result in an increase?

A. Yes.

Q. And when Mr. Strathy was asking the questions earlier and you indicated it might be as much as double, were you referring to the study which is the substance of that abstract?

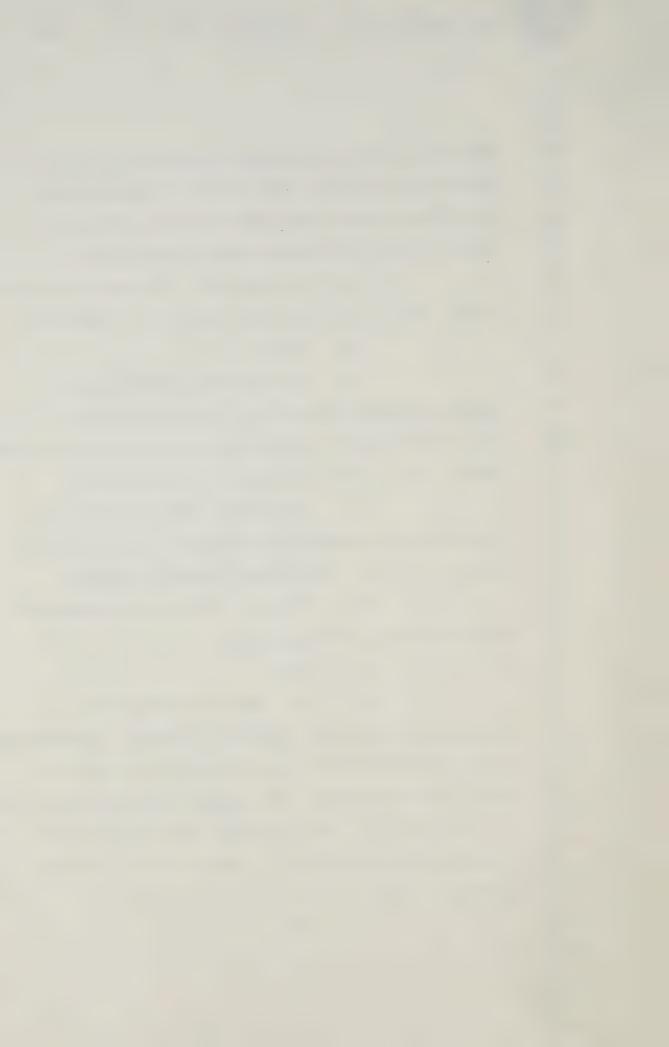
A. The actual values which are given here for indomethacin resulted in an increase from 2.2 to 3.2. Those were the mean increases.

Q. That is right in the middle of the paragraph, is that right?

A. Yes.

Q. Mr. Hunt, who immediately preceded me, asked you about Mr. Cimbura's methodology and I understood you to say that while you do not have a lot of data but have simply general information at this point in time, that there were some aspects that you would not like to comment on now but some that you could?

. That is correct.





Q. Mr. Hunt did not ask you what
you could comment on so I am now asking you what
you feel comfortable to comment on about Mr. Cimbura'
methodology?

A. There were several areas. The one area would be, if my understanding is correct,

Mr. Cimbura indicated that he did not make a correction for recovery studies which he said that he performed.

THE COMMISSIONER: Did not make a correction for the recovery?

in other words, the recovery as measured apparently in his studies, I have not seen his data, but he stated that the recovery in his studies was below 100 per cent. I think he mentioned a figure of 85 per cent and again my comment there would be that I think it is appropriate to correct for losses in an analytical procedure.

When we do similar studies on the drugs which we measure if the recovery is, let us say, 50 per cent, then we make such a correction.

It is very important, talking about recoveries, to know whether or not a recovery is consistent from sample to sample. So that one, when one then deals with an unknown sample, one can use



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the correction factor. So if we take let us say, 10 samples of whole blood from different people and if we found that the recovery of digoxin from these samples was 85 per cent in every case then we could correct by 100 over 85 in the unknown samples because we would have some data showing that the recovery of digoxin was consistent from sample to sample.

If we do not have that data then

one cannot - one does not know. On the other hand,

if the data showed that the recovery varied from

sample to sample, then it would be extremely difficult

to make a meaningful correction.

Q. Are there any other comments you can reasonably make at this point in time about Mr. Cimbura's methodology?

A. Well, two small comments - if I recall he stated that recovery studies of some sort had been carried out on blood and tissues but not on ærum. I think that is what he said. I think that in my opinion one should always carry out recovery studies on, let us say, serum, if one is then going to report results on serum so that if we intend to develop a method which can be used for the quantification of digoxin in serum we should have



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assessed its recovery in serum. If we are going to use that method for the measurement of digoxin in whole blood, we should have assessed its recovery in whole blood and if we are going to use it for the measurement of digoxin in heart tissue we should have used it to do recovery studies in heart tissue. As I have indicated, again these are my personal views, I think one should do several studies showing that the recovery does not change from sample to sample.

Getting away from the recovery area,
my experience with saline standards, which I think
Mr. Cimbura stated that he used, although the point
when he switched from serum standards to saline
standards is not at all clear to me, from what I heard.

But my impressions of the use of saline standards, again I would think that the standards should be in the same matrix as the samples that have been tested. That is, if we are testing samples in serum then the standards should be in serum and if we are testing samples in whole blood the standards should be in whole blood.

If this does not occur, my experience with the RIA procedure, shall we say, as used at Sick Children's, is that errors may arise as a result



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of using saline standards instead of serum-based standards in the analytical procedure.

That is true not only for digoxin but it is true for many assays so wherever possible we use standards which are in the same matrix as the samples being analyzed.

You used the word "matrix" and 0. for those of us who are novices, that simply means the substance into which you put the digoxin for the standard?

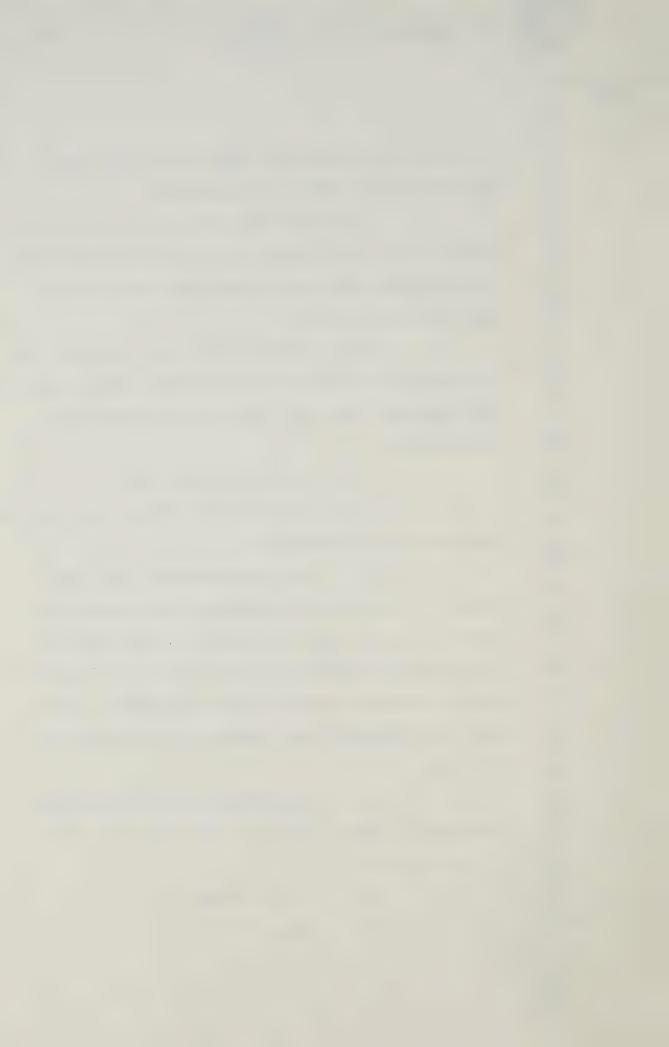
- That is right, yes.
- Q. On this very point, have you done some work at the Hospital?

We have developed many drug assays. If you are talking about with respect to digoxin, we have done, obviously we have looked at the factor of using saline standards versus serumbased standards in many of our drug assays, but we have also looked at with digoxin in respect to the RIA assay.

Specifically on the RIA assay Q. of digoxin, have you analyzed the effect of saline in the standard?

In our assay?

Q. Yes.



A. I would point out that the situation in Mr. Cimbura's lab might be completely different. He may well have evaluated saline standards fully and found that they are the best type of standards to use for his particular assay, I do not know.

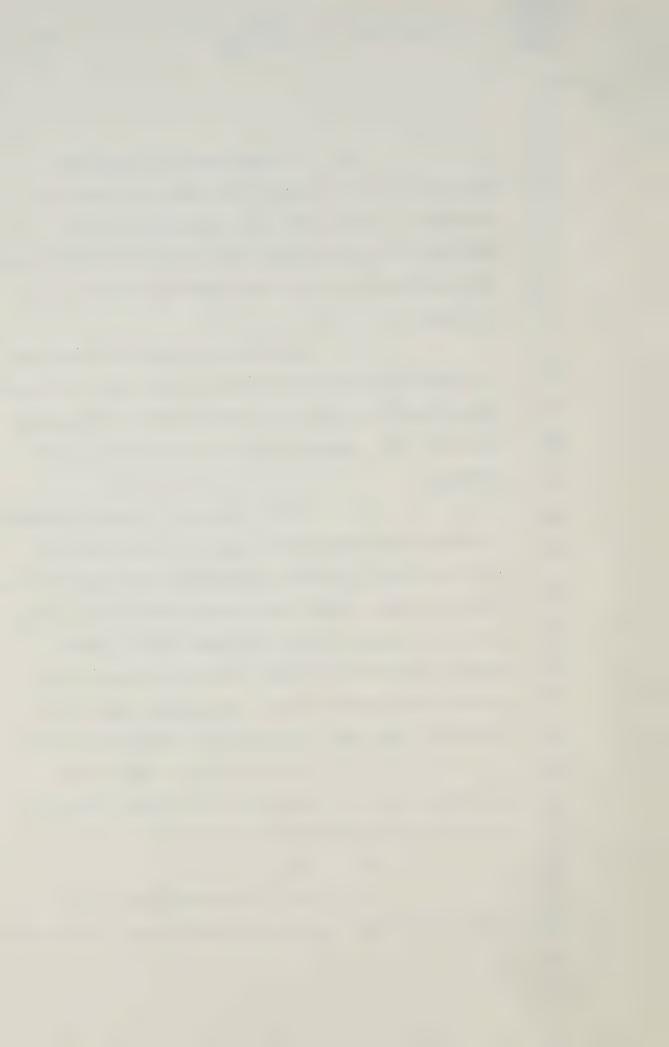
Q. Assuming we enquire of him when he is next here whether he did or not, for the moment can you tell us about the conclusions of the testing that you did, comparing the saline matrix for the standard?

A. In our system it caused a skewing, is perhaps the best way to say it, of the standard curve so that it changed essentially the slope of the standard curve. What this would give rise to in our particular system is that we would have reported results which were too high in the low areas of our standard calibration curve and results which were too low in the high areas of our calibration curve.

Q. Can I use some numbers to illustrate that, Dr. Soldin? Am I correct that you were measuring on a calibration of 0 to 5?

A. Yes.

Q. Do I understand that if you measured and got a reading between 0 and 2 that because





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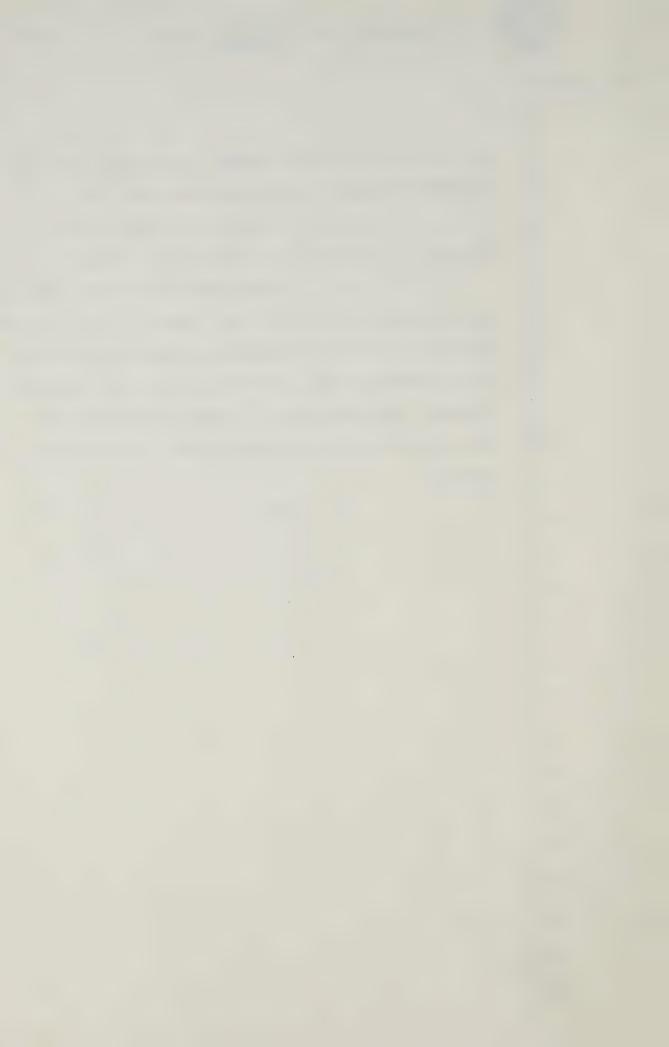
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of the saline that the result was falsely elevated and that it ought to be something like 1.5?

It could have been out by as A. much as a factor of 1.5, yes, in our system.

I just want to simplify this as much as possible and use some numbers. Am I accurate in saying that if you tested and got a result of 2 that because of the saline factor the more accurate reading ought to be 1.5 - ought to be with some deviations - but it is lower than 2, that is the point?

> A. Yes.



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		Q.		And	if,	on	the	other	hand
you meas	ured a	nd got	a	read	ing	of	four	: that,	, in
fact, it	ought	to be	pe	erhap	s 4.	.5 c	or 53)	

That's correct, yes. A.

Now, is there any written 0. summary or report about this analysis of this saline effect that you conducted in the hospital?

No, there is no written summary or report on that.

MS. KITELY: Those are all my questions sir.

THE COMMISSIONER: All right.

Ms. Jackman, are you now ready? CROSS-EXAMINATION BY MS. JACKMAN:

Doctor, I just have a couple of short questions following up from Ms. Kitely. She was talking about the testing using saline standards. If you were using an extraction process before you tested such as, HPLC and RIA, do you think that would have any effect on the distortion

A. Well, an extraction process would effect first of all the recovery, and this is what we are really talking about in Mr. Cimbura's case. From the evidence it's not clear

that you've talked about?

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whether Mr. Cimbura uses the extraction process for his saline standards as well as for his patient samples. He may and he may not, I am sure that will come to light later.

Q. Doctor, have you ever tested tissue samples?

A. No. Well, as long as you don't call blood a tissue.

Q. Are you familiar with the literature or the methods of testing tissue samples?

A. I am not a forensic scientist,

I'm a scientist who has had a fair amount of experience
in the measurement of drug concentrations in biological fluids, not in tissues.

Q. Well, Doctor, would you be able to, based on your experience, say what the concerns would be around analyzing tissue samples, what steps you would have to go through in order to make sure you got accurate readings?

A. Well, I have never analyzed tissue samples. So, I would rather address myself to something that is perhaps close to that but not the same as it, which is, what study should be carried out in developing a method for serum or plasma, which I have had a lot of experience with, and can





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talk about very competently. Now, if you don't want to hear that then I won't go further.

MS. CRONK: Well, Mr. Commissioner, I don't like to interrupt my friend's cross-examination, but the witness has already disclaimed any experience in tissue testing, not once but a number of times throughout his evidence and I would have thought that any questions directed to the appropriate ness of a particular system versus another for tissue testing is something that Dr. Soldin candidly and immediately recognizes as beyond his purview and experience.

MS. JACKMAN: I will leave it, Mr. Commissioner.

Just one other question. Have you ever tested whole blood? I should put it this way. Would you have any concerns about testing whole blood in terms of readings of digoxin?

> Α. In terms of?

0. In terms of getting an accurate reading of what the level of digoxin is.

Well, I noticed the forensic literature uses whole blood a great deal. I think there are certain problems attached to the measurement of digoxin concentrations in whole blood and I





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think it would depend on how that sample is treated.

Digoxin itself binds to the red cell and the red cell membrane fairly strongly. The extent of its binding, certainly is different and upon the age of the patient, as opposed to the digoxin binding in serum, which is very weak. So that if one performed an extraction procedure from serum, I think you might, I am not saying you will, but you might get a different recovery for digoxin from serum than the recovery that you would obtain from whole blood, in which digoxin is bound to membrane. The recovery that you get from them all might be dependent on how much digoxin is, in fact, bound to that membrane which varies, as I pointed out, with the age. It might vary with the length of time that you were to use in the actual extraction procedure. Let's say you were using an organic solvent such as dichloro methane. Those are the only comments that I have to make on that.

Q. Could I just ask you one further question on that. When you are talking about the differences in using whole blood or serum, would the results likely be higher if you



were using whole blood or lower?

A. I don't want to go any further than I have already gone.

 $$\rm Q.$$ Okay, those are all the questions that I have.

THE COMMISSIONER: Thank you.

Mr. Young?

MR. YOUNG: Mr. Commissioner, I indicated earlier that I didn't have any questions, but there is one matter that has come to light.

THE COMMISSIONER: Yes, all right.

CROSS-EXAMINATION BY MR. YOUNG:

Q. Dr. Soldin, in response to one of Miss Kitely's questions, you stated that Mr. Cimbura did not make a correction for the amount that he recovered. I believe that is referring to the extraction process, is that right?

A. That's my understanding. I may be wrong, but that's my understanding.

Q. Would it be correct to say,

Doctor, that without this correction factor or

process that any results that were received would be
underscored?

A. They would be lower, yes.

THE COMMISSIONER: I am sorry?



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THE WITNESS: They would be lower.

THE COMMISSIONER: Lower.

MR. YOUNG: That's the only point I wanted to make, thank you.

THE COMMISSIONER: Mr. Ortved.

MR. ORTVED: Thank you, Mr.

Commissioner.

CROSS-EXAMINATION BY MR. ORTVED:

Q. Now, Dr. Soldin, as I understand it, you are the last witness in this preliminary phase concerning digoxin. I would just like to summarize, if I might, very briefly, for the assistance of all of us and for the Commissioner, those cautions which as a biochemist and as an expert you feel have to be applied in interpreting levels of digoxin. Firstly, as I understand it, you have to firstly consider what the sample is, is that correct?

A. Right.

Q. And you told us, and I don't intend to repeat this, that you have to bear in mind, firstly, is the sample one of serum, plasma or whole blood, right?

A. Yes.

Q. And bearing in mind which it is, that may, to some extent, skew the results.



		Α.	I	am	not	aware	of	the	differ	ence
between	serum	and	plasma	in	the	measu	ceme	ent o	of	
digoxin.										

Q. Right, but as between serum and plasma on the one hand and whole blood on the other, you may get a skewing of the results.

A. You may, although I am not basing that on my personal experience.

Q. I understand that. I am putting my questions to you not just on the basis of your experience, but on the basis of your understanding of the literature, all right?

A. All right.

Q. Then, secondly, in terms of samples, under that first heading of samples, you have to be careful as to whether it's a sample of fluid or a sample of tissue, correct?

A. Right.

Q. Because, as we have heard here, if it is a sample of tissue, digoxin binds differently to different tissues and you can get very high readings from certain tissues.

A. Right.

Q. And, in particular, the readings for the myocardium may be in children as high as



340-odd times that in the serum?

A. The best person to talk about that is Dr. Speilberg, I think.

Q. But that's what the literature

A. Right.

THE COMMISSIONER: Yes, Ms.

Cronk.

says.

MS. CRONK: Excuse me, Mr. Ortved.

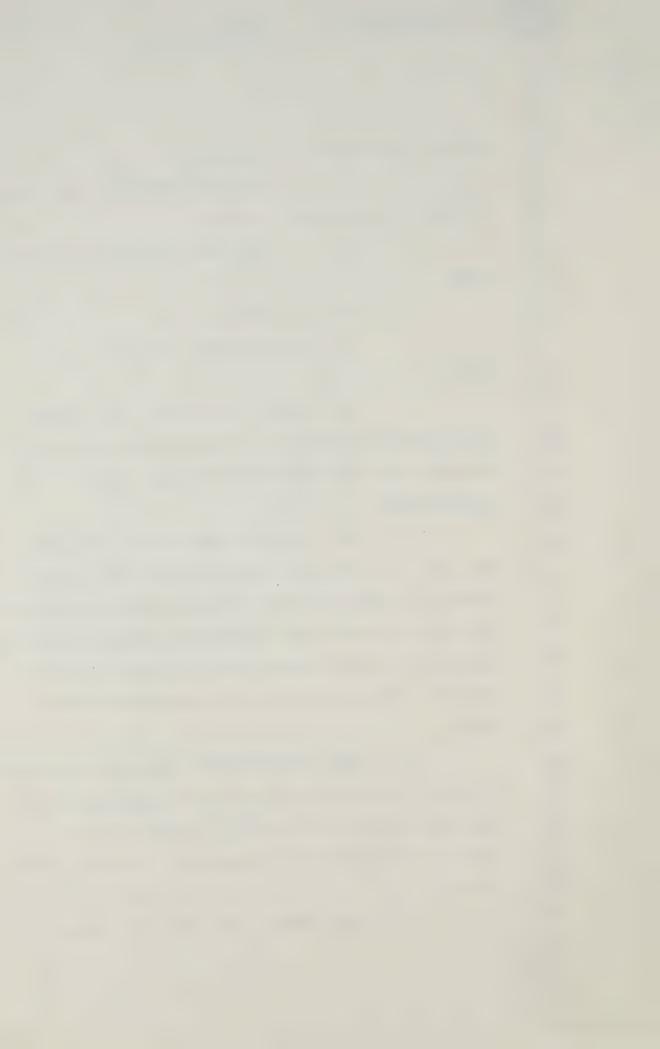
Again, with hesitancy I interrupt, but I have two
problems with the line of questioning, Mr.

Commissioner.

The first is, once again, and I did not rise at my friend's first question but at the second, it seems to me he is now moving into the area where he is asking this witness to comment on matters related to tissue testing and experience on tissue testing. Again, we have had a disclaimer from Dr. Soldin.

THE COMMISSIONER: Well, he's not going that far. All he's saying, it is a question to be applied whether it is fluid or tissue, which is the sort of question if he asked me I think I could answer.

MS. CRONK: Well, but the second



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difficulty or the color to the issue, Mr. Commissioner, and perhaps simply it can be made clear ---

THE COMMISSIONER: When it gets into precisely what the difference is, then I will stop him, but right at the moment he is merely saying that you apply some caution if you don't interpret figures for fluid and tissue the same way.

Mr.Commissioner, is that Mr. Ortved introduced this line of questioning by speaking about the interpretation of results and Dr. Soldin has said on any number of occasions that that, again, is not a matter that is within his experience or, indeed, within his responsibility and if he is being asked to comment in that context with that preface on question of this kind, I have a great difficulty with him being permitted to do so.

THE COMMISSIONER: Yes, all right.
Well, I won't be taking it that way, though, Mr.
Ortved, so you carry on.

MR. ORTVED: Thank you, Mr.

Commissioner.

Q. Then under my second heading
I have site of the sample. I take it in your
experience and as a biochemist that is something



that has to be carefully considered.

A. It depends what sample you are talking about. If you are talking about autopsy samples, it is important.

Q. That's right.

A. If you're talking about samples drawn from an intravenous puncture or from a capillary heel stab or finger prick, I think there is very little difference between the latter three.

Q. Right. But speaking of autopsy samples for the moment, and autopsy samples in serum obtained on autopsy, the site from which that sample is taken is of importance, correct?

A. The literature would indicate that, yes.

Q. Right. And then, thirdly, as I understand it, and you have talked about this very recently in your evidence, the time after the administration of the dose is of importance?

A. It's crucial.

Q. Right.

And that can vary particularly depending upon whether the dosage is intravenous or oral.

A. Oh, I think what I said was it



was independent, essentially, of whether the dosage was IV or orally, that one should wait for the ideal sample, which is the pre-dose sample in both cases.

- Q. Precisely. But depending upon whether the administration is intravenous or orally, that can have an effect if the sample is taken before equilibration is reached.
 - A. Certainly.
- Q. Then, fourthly, and this is something that you probably know from the literature as opposed to your own experience, whether the sample is ante mortem or post mortem is of importance.
 - A. Right.
- Q. And if it is post mortem there may be a factor involved?
 - A. Yes.
- Q. Fifthly, the age of the subject is of importance.
 - A. In what regard?
- Q. Well, in the regard that we have heard here from Dr. Seccombe and from yourself that there may be non-dig like substances that may impact on results.
 - A. Correct.





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Yes. Α.

Q. That is something that has to be looked at and if possible, eliminated?

> A. Right.

And then lastly, something Q. we have heard a great deal about here, the actual test itself may be a factor?

A. Yes.

Q. There is a variation between the accuracy of tests.

A. They could be, yes.

MR. ORTVED: Those are my questions.

Thank you.

THE COMMISSIONER: Miss Solomon.

MS. SOLOMON: No questions.

THE COMMISSIONER: Mr. Olah.

CROSS-EXAMINATION BY MR. OLAH:

Q. Just following up on a question, Doctor, that was asked of you. As I understood your evidence the absence of factoring in 85 per cent instead of 100 per cent recovery level means that you are actually getting low levels of readings



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rather	than	the	true	higher	accurate	levels?

- A. That is if one makes an adjustment for recovery as I state it. The issue though is one of there is a further complexity to this problem. That is does Mr. Cimbura employ an extraction procedure for standards, that is the same procedure that he employs ---
- Q. I'm sorry, could you repeat that?
- A. Does he employ an extraction procedure on standards that is the same procedure that he employs when he does analysis on tissues or blood. You know, if he does employ an extraction procedure on standards maybe the extraction is different.
- Q. Are you suggesting that there should be an extraction procedure applied not only to the sample but to the standard also?
- A. I am suggesting again I want to get away from tissues now and talk about serum and plasma which I have had experience with. If I wasn't making an extraction procedure for the isolation of a drug from serum or plasma that ideally my standard should follow the same route of analysis.
 - Q. Following that line of logic,



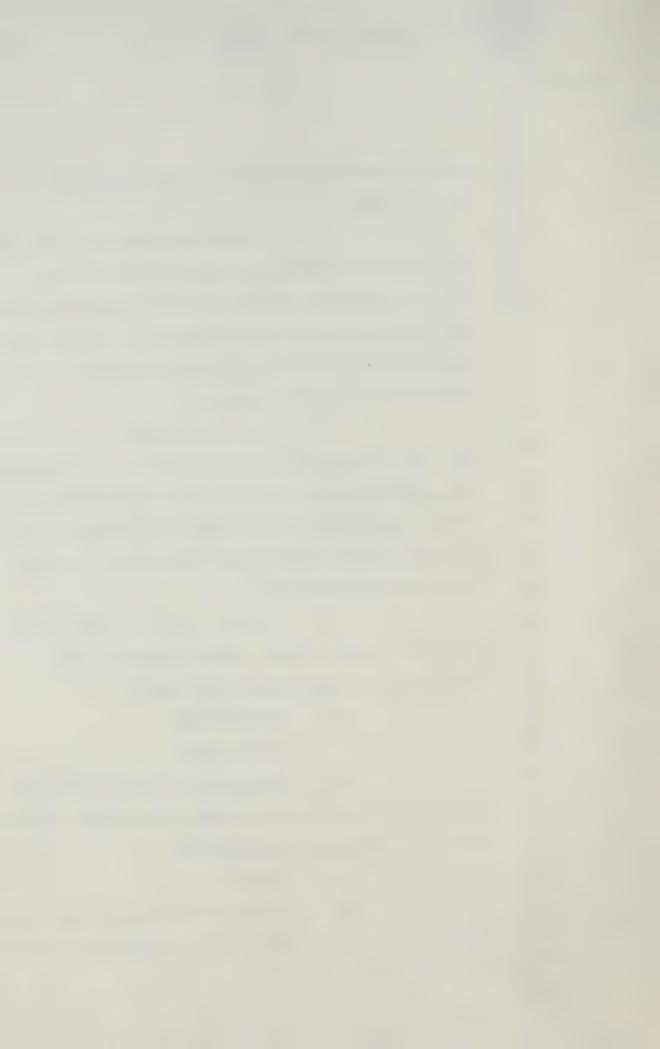
are you suggesting that HPLC should also be done to the standard?

are going to standardize your system then the standards must go through the exact procedures that the samples go through and ideally the standards, in my experience, should be in the same matrix as the substance as you are testing it.

Q. Now, getting back to that issue that was raised with you by Miss Kitely. I understood your evidence to be that in effect that the higher ranges the use of saline instead of plasma or some fluid in essence understated the results. Do you remember that evidence?

A. I said - well, it depends what you call a higher value, values between 3 and 5 were falsely, would be falsely lower.

- Q. Understated?
- A. Understated.
- Q. What about if we were dealing with levels substantially higher say in the range of 60 or 70 nanograms per millilitre?
 - A. Right.
 - Q. Could you help us in that regard?
 - A. Well then you would do a dilution



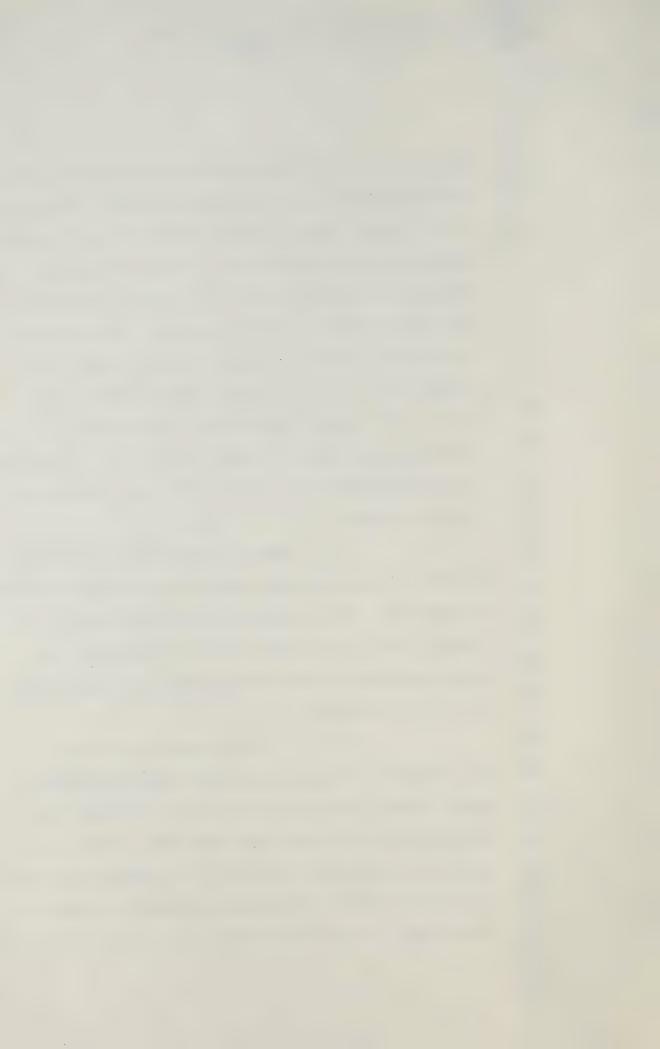
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in order to get the sample to read within the zero to 5 because that is your calibration curve, if you have a calibration curve that goes from zero to 5, if the sample reads 60 you have to dilute that sample, depending on what dilution you choose your answer then might differ. If you choose a dilution that gives you a result of 3.5 that would - and I am talking about our particular assay system, that should be in other words higher than using the procedure that we use, higher than 3.5. If one got a result between zero and 2 that result would be falsely higher.

Q. What I am trying to determine is this. Is there some sort of a multiplier effect, or some sort of an impact when you are looking at fairly high levels, that is the difference, the use of saline, is that magnified as you get higher, or is it a constant?

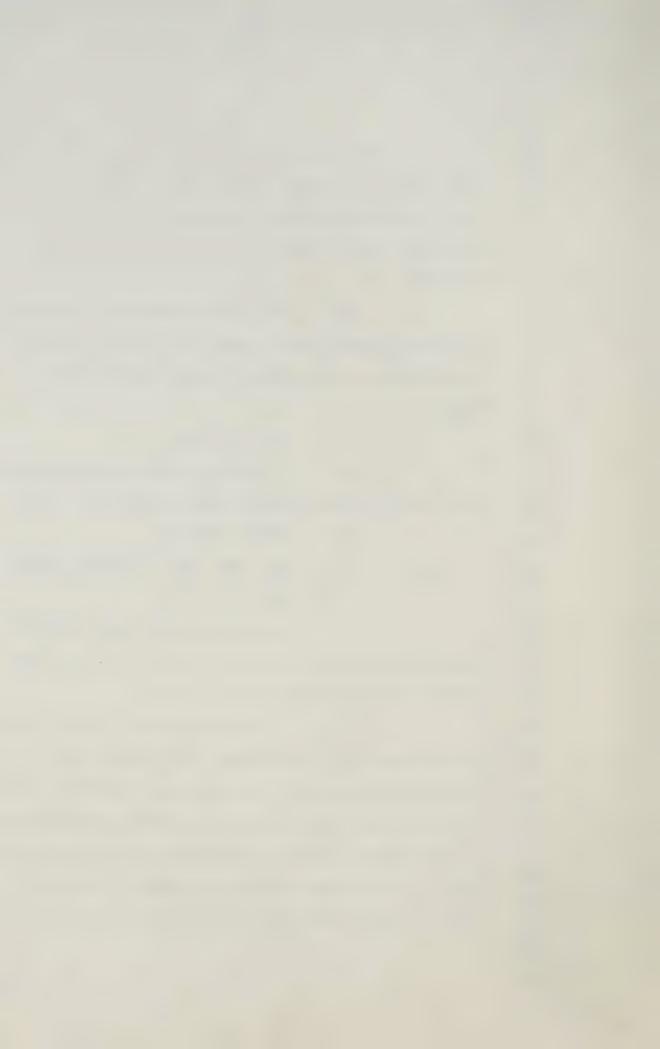
A. I can't answer that for Mr. Cimbura's situation and for the experiments which he has done. All I can do is address that question to the studies we have done. What I am trying to indicate to you is that whether the result is falsely high or falsely low depends on where it would fall in our calibration curve. If it fell in



the lower range of our calibration curve, right, it would be falsely high. If it fell in the higher range it would be falsely low, now that is in our particular assay, and the situation may be quite different ---

- Q. As I understood your evidence the time it takes you to carry out an RIA sampling is somewhere in the range of about two to three hours?
 - A. An RIA, yes.
- Q. I think you have also indicated that you have had extensive experience with HPLC?
 - A. That's correct.
 - Q. But that was in non-dig situations?
 - A. Yes.
- Q. Bearing in mind that experience, how long do you feel that an HPLC application with respect to dig would normally take?
- A. I have never done one so I would have to draw on my experience with other drugs.

 Assuming that one does an extraction procedure, which we do for many other drugs, followed by evaporation of the organic solvent, followed by chromatographic state, I think that the HPLC procedure certainly can be accomplished within perhaps an hour for a



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single sample.

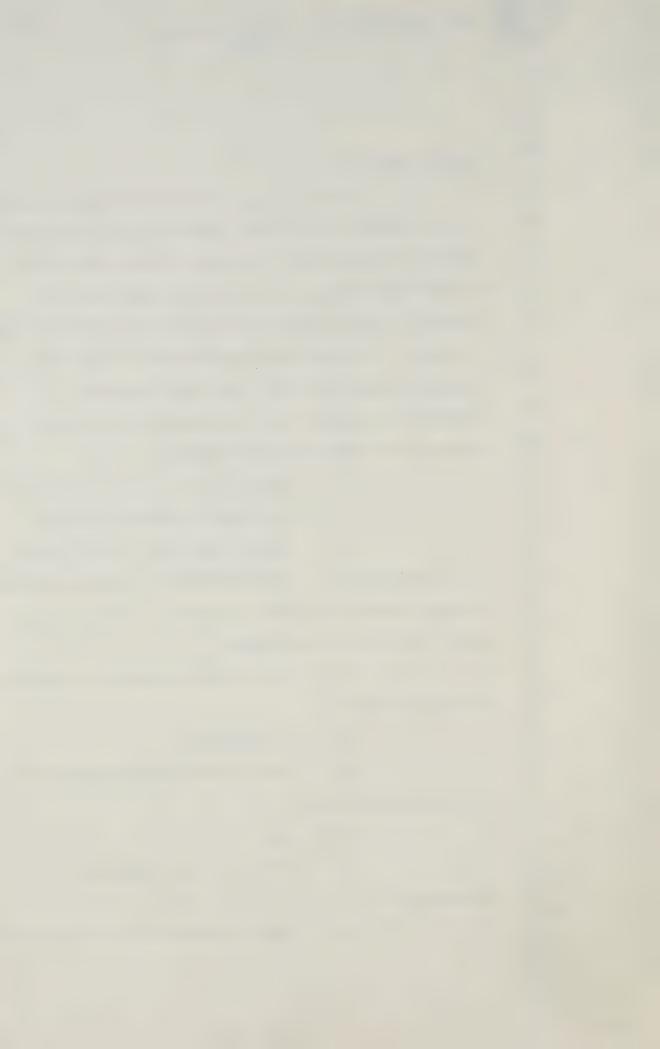
Q. Were you here for the evidence of Mr. Cimbura in which he indicated that it normally took him somewhere in the range of one and a half to two days to carry out this two-step process, bearing in mind there was also an extraction procedure in there? Is there any explanation - maybe we should go back one step, how long would the extraction process - are you familiar with the extraction process he talks about?

A. Yes.

- Ω . How long a process is that?
- A. Well, I am not, I don't know how he applies it. The extraction process is using organic solvents and they tend to be fairly quick, short extraction procedures.
- Q. He was extracting as I understand for metabolites.
 - A. I am sorry?
- Q. He was extracting metabolites as I understand here?
 - A. Yes.
 - Q. And also other dig-like

substances?

A. Well, whatever he is extracting.



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But any extraction procedure you know we use one for example when we measure theophylline by HPLC. You take a sample, you add the organic solvent, you vortex it or shake it, that is the equivalent for a certain time period. You centrifuge, you then separate the organic solvent and you then evaporate that. Now for the majority of solvents that whole procedure can be accomplished easily within 30 minutes.

- Q. 30 minutes?
- A. For the majority of solvents, not for all.
- Q. I guess what I am driving at is this. Given the time spans that you have mentioned to us today, do you have any explanation as to why it would take Mr. Cimbura one and a half to two days to carry out the totality of the procedure?
 - A. No, I have no explanation.
 - Q. Does that strike you as

unusual?

A. I don't know what he is doing.

I would say in my laboratory it would be strange.

MR. ORTVED: Thank you, Those are

my questions.

THE COMMISSIONER: Mr. Shanahan.



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CROSS-EXAMINATION BY MR. SHANAHAN:

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Just very briefly, sir. As I understand it here, if I were to come to you in the hypothetical and tell you that Dr. Cimbura has come up with, or had come up with a very high digoxin reading. Based on the observations that you have made with respect to his methodology here, would I be right in concluding then that even that very high reading, because of two factors that we will go into, that very high reading may even be inaccurate insofar as it is just too low?

There are - it may be too low. I think there are certain circumstances which possibly may cause it to be too high but I cannot address those because I don't know enough about Mr. Cimbura's method.

Q. What you do know, if you were for instance to have an average recovery rate of 85 per cent, if you were to correct that, that would be one factor that may make those high readings even higher?

Correct.

And second of all here, with Q. respect to the use of the saline standards that you made comment on, that the high readings got off the



saline standards may in fact also be skewered to the effect that they were made too low?

A. Well. depending how he trea

A. Well, depending how he treats the saline standards, and depending on the recovery from the saline standards, the results may be too low or too high, that is why I am edging on that one. I don't know what he does and I would rather not address the issue until I do know what he does.

- Q. One final thing then, you can't, as I understand it, on the calibration you have got, you cannot get a reading we will say of 60 or 70 nanograms, what you do is you get a reading between zero and 5 and because of the dilution process you are able to get a final exact reading, is that right?
 - A. Yes.
- Q. You said it was out by a factor of 1.5 possibly, would that be of a diluted sample?
- A. That is on the diluted sample, it would then be multiplied by whatever the dilution factor is.
- Q. All right, my question then is as you would multiply to eventually get your reading we will say of 60 or 70 nanograms are you not then also multiplying that error factor of 1.5?
 - A. Well, let's take a hypothetical



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example. If you had a concentration of 2 and had the dilution factor of 20 then that should be 40 nanograms per millilitre.

> 0. Yes.

A. If indeed that was falsely high and the results should have been 1.5, then the two results should be in fact 30 nanograms per millilitre instead of the 40 nanograms per millilitre which is the one that you would have found.

0. So that is an area where it would be falsely high?

Yes.

MR. SHANAHAN: Thank you, sir, I have no further questions.

THE COMMISSIONER: Mr. Labow.

CROSS-EXAMINATION BY MR. LABOW:

Dr. Soldin, if I understand Q. your memorandum to Dr. MacLeod, one of the reasons you favoured the FPIA method over the RIA method has to do with the American Association for Clinical Chemistry Study that you included as your last page.

THE COMMISSIONER: What is the last

exhibit?

items.

THE WITNESS: Yes, that is one of the



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MR. LABOW: Q. If I could just refer to that page for one moment.

THE COMMISSIONER: Which exhibit

MR. LABOW: Exhibit 25.

- Q. Now the criticism that I drew from your evidence is that there is a much wider scatter using the RIA method and a greater variability?
 - A. Between the laboratories, yes.
 - Q. Between the laboratories?
 - A. Yes.
- Q. Could the fact that nine times as many laboratories reported using the RIA method account for the fact that there was a much greater scatter? In other words, some of those laboratories were not terribly proficient?
- A. Yes, it would account for a difference in the minimum and maximum values that the standard deviation would take into account the number of the laboratories and so that would sort itself out so to speak.
- Q. But wouldn't the identical mean result indicate that basically these two tests give the same results?
 - A. In good hands the two tests



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give the same result on that sample.

MR. LABOW: Okay, that's fine,

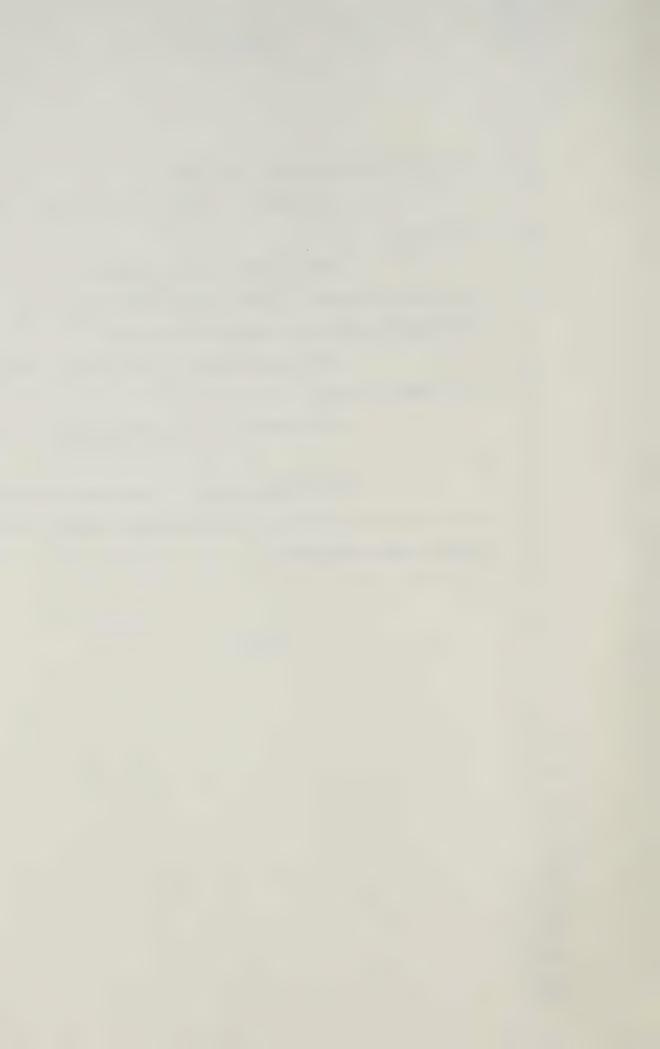
thank you.

Now, I do have one question for Commission Counsel. Is Dr. Soldin going to be returning to give any specific results?

THE COMMISSIONER: He doesn't have any I don't think.

MR. LABOW: I thought he did have one.

THE COMMISSIONER: My understanding is he did not do any of the tests upon the babies with which we are concerned.



THE WINTESS: I did none of the tests but I was on call on one of the weekends when two of the children died.

MR. LABOW: And you supervised?

THE WITNESS: And therefore was

involved in supervision over that one weekend.

MS. CRONK: That is my understanding, Mr. Commissioner; and we may need to bother Dr. Soldin again, if that is the case.

THE COMMISSIONER: The answer to that is "maybe" then I guess.

MR. LABOW: My only question for the Doctor is, if we have heard further from Mr. Cimbura regarding his data and his methods, and you do return, I presume you would then be in a position to comment on the overall methodology that he used.

THE WITNESS: Yes, if you ask me.

MR. LABOW: Thank you.

THE COMMISSIONER: I was sort of hope that we would get rid of this general discussion on digoxin at some point, but perhaps not.

Mr. Roland?



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	MR.	ROLAND:	I	have	no	questions,
Mr.	Commissioner.					

THE COMMISSIONER: And now what do you say? Can we complete this before we all die of starvation?

MS. CRONK: I'm going to be a little while. I suggest we return and do it after lunch, Mr. Commissioner.

THE COMMISSIONER: How long do you think you will be, about half an hour?

MS. CRONK: Yes, I would think so.

THE COMMISSIONER: What do you say

we come back at 2:00 then?

MS. CRONK: That is perfectly

acceptable, Mr. Commissioner.

THE COMMISSIONER: Is that satis-

factory to you, Dr. Soldin?

THE WITNESS: Yes.

THE COMMISSIONER: All right, we

will come back at 2:00 then - sorry - yes?

MR. LAMEK: Mr. Commissioner, just so that I know what I am about for this afternoon, if we return at 2:00 and we are completed at 2:30 may I suggest that we not embark upon a new witness on the last hearing day of the week.



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You are quite right, Dr. Soldin is for the time being at least the last of the witnesses on the general area. Dr. Mirkin has to come back. We may hear from Dr. Speilberg; but I propose with the next witness to start getting into numbers of deaths and then immediately thereafter into the medical review of charts and medical evidence of that kind. I would suggest, sir, that it might be more appropriate to start that whole new block of evidence on Tuesday morning, whatever time we end this afternoon.

THE COMMISSIONER: I downot think you will find too much objection from anyone to that proposal. As I do not see the immediate end of this Inquiry, I will not object myself.

Is there anything else that you want to say? Do you want to tell anyone else - or are you distributing a program of the evidence for next week?

MR. LAMEK: No, it is really quite easy, though, Mr. Commissioner. I can announce it now.

I propose on Tuesday morning, in light of what you have just said, to call Dr. Anne Gilmour-Bryson who is a consultant to the



Commission, not a medical doctor, and she will give evidence and introduce some charts based on information supplied by the Hospital as to the number of deaths on the Cardiology Wards and the Cardiology Service in the period in which we are interested and in the two immediately preceding nine month periods and the two immediately subsequent nine months periods.

Then I propose to call Dr. Richard
Rowe who is the head of the Cardiology Division
of the Hospital for Sick Children and who is among
the very first people to review charts in the
period and to form an assessment as to the explainability of the deaths.

THE COMMISSIONER: Dr. Soldin, thank you, and you are free now - no, you are not quite free, you are free until 2 o'clock if you want to go off. Come back at 2:00 for a grilling by Miss Cronk.

MR. LAMEK: I will be taking

Dr. Rowe through a number of the charts that he

reviewed over the course of the late summer, early

fall of 1980 and early 1981, and the subsequent

chart reviews that he did, and I have every expectation

that I will be at least three hearing days with



Dr. Rowe in chief.

THE COMMISSIONER: Yes, all right.

That will certainly occupy us next week and probably the week following.

MR. LAMEK: It certainly will, sir, but we will be starting on evidence now going to particular deaths that are at issue.

THE COMMISSIONER: All right.

Whatever happened to the expurgated Atlanta Report?

MR. LAMEK: It has been discretely distributed to counsel, sir.

THE COMMISSIONER: All right, thank you.

Yes, Miss Kitely?

MS. KITELY: Mr. Commissioner, in light of the evidence of the consultants concerning these deaths in the five periods outlined, I'm assuming that there is some material that is available from which she is going to give evidence. Might we have it this week, as opposed to when she gets in the witness stand? I think it is something that we are all very interested in.

MR. LAMEK: Mr. Chairman, if what Miss Kitely is suggesting is that she gets copies of the charts before the end of the week, I do not



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have any difficulty with that. On the other hand, she is not going to be able to do very much to verify the accuracy of the charts because that is a whole mass of documentation that has been inspected by Dr. Bryson at the Hospital. But for every use the charts may be, there is no reason why this should not be made available, tomorrow, I think.

MS. KITELY: Thank you.

THE COMMISSIONER: Anything else?

All right, then, until 2 o'clock.

---Luncheon recess.





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--- Upon resuming.

THE COMMISSIONER: Yes, Ms. Cronk?

MS. CRONK: Thank you, Mr. Commissioner.

REDIRECT EXAMINATION BY MS. CRONK:

Q. Dr. Soldin, we are nearing the end. I promise I won't keep you much longer.

You will recall that this morning during cross-examination I believe it was Mr. Strathy's cross-examination, you indicated, according to my notes, that it was only in recent years that the FPIA technique had become available for drug concentration assays. Do I have that correctly?

A. That's to the best of my knowledge, yes.

Q. All right. Can you help me,
Dr. Soldin, because I wasn't clear in that exchange,
to the best of your knowledge, when did the FPIA
technique first become available for digoxin
assays?

A. I don't know that I can answer that question properly. I think probably around two years ago.

- Q. All right.
- A. But one year ago we evaluated



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ago?

Q. At your own hospital a year

A. Sick Children's, right.

Q. Well, perhaps I could put the question this way. During the period July, 1980 to March of 1981, to the best of your knowledge, was the FPIA technique then commercially available on the market?

A. No, it wasn't available.

Q. It was not, thank you.

Dealing still with the FPIA Method in light of the cross-examination this morning, Dr. Soldin, can you tell me this, if you are able: in your opinion, had the FPIA technique, as you now know it, been available during the period July, 1980 to March of 1981 and had been used instead of the RIA procedure to conduct digoxin assays on the children with which this inquiry is concerned, would you expect, or would you have expected any material differences in your readings that might have resulted?

A. You are talking about the samples that were analyzed by the Hospital for Sick Children, I take it?



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Yes, I am. Q.

I would anticipate that the Α. results would be fairly similar.

Thank you. And you were 0. questioned this morning as well by Mr. Strathy, I believe, concerning the HPLC method and, specifically, he drew your attention to Exhibit 25 which, as you will recall, is a copy of your memorandum to Dr. MacLeod and the last page of that exhibit. It might help you to have it before you.

> Α. All right.

I am referring, Mr.

Commissioner, to the last page of that exhibit.

As I understood your evidence, both in respect of questions put by Mr. Strathy and earlier, Dr. Soldin, the laboratories indicated on that chart, if I could call it that, are a reflection of those clinical laboratories which are members of the association that produced those recorded data. Is that correct?

That have enrolled in this Α. program. They would all have enrolled in the Therapeutic Drug Monitoring Program of this association.

> Q. All right.





But I had understood, and perhaps
I have this wrongly, I had understood your evidence
to be that you could not help Mr. Strathy as to how
many, if any, forensic laboratories that might or
might not be members enrolled in that program, is
that correct?

A. I cannot help him without asking the people in Washington that question.

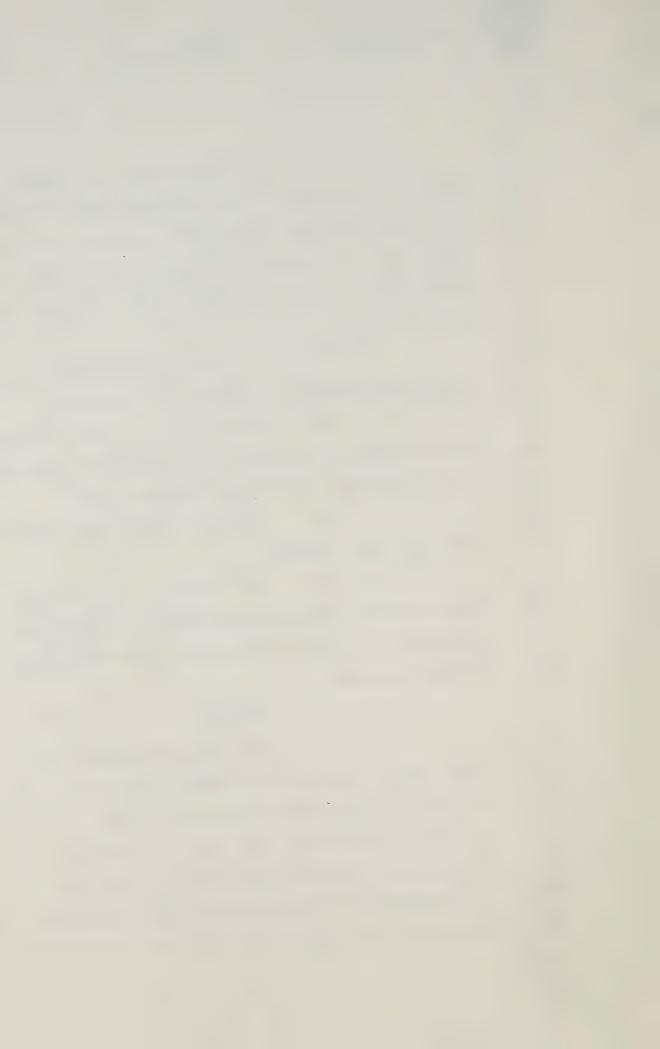
Q. All right. Do you know here today whether or not any forensic laboratories are in fact members, quite apart from how many?

A. I don't. But I would doubt that many are, if any.

Q. Do I take it that you have doubts in that regard because this is a membership program set up with a therapeutic drug monitoring purpose in mind?

A. Correct.

Q. All right. We should not, then, would I be correct in suggesting, Dr. Soldin, take the numbers disclosed on that chart as being indicative of the number of forensic laboratories that may or may not be using the RIA method or the HPLC method or any of the other techniques outlined on that chart for the purposes



Soldin re.dr. (Cronk)

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of digoxin assays?

A. Right.

Q. The numbers for forensic laboratories may be quite different?

A. Yes.

Q. Thank you. You also indicated, as I understood it earlier in your evidence, Dr. Soldin, that it would be unusual to couple HPLC with the RIA technique for detection, did I note that correctly?

A. It's not commonly employed as a detector for HPLC, yes.

Q. And did I also note correctly that you indicated to Mr. Strathy that that combination, if linked together, was a very sensitive process?

A. If linked together it would provide sensitivity perhaps comparable to the RIA procedure, perhaps a little less, because you get dilution of the sample as it progresses through the column. So, RIA is a sensitive procedure.

Q. I am sorry, perhaps I put
the question badly. My question to you was, I had
understood you to say earlier this morning that if
one were to use RIA as a detection method in association



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with HPLC, I had understood you to say that that combination would be a very sensitive procedure or process.

- A. Right, it would be, yes.
- Q. Can you help us today, or do you have any knowledge, Dr. Soldin, as to the number of forensic laboratories in North America that are, in fact, using that combination for digoxin assays, or do you know?
 - A. I have no idea.
- Q. Thank you. And dealing with the technique that's been described as HPLC MS, mass spectrometry.
 - A. Yes.
- Q. I believe you told Mr.

 Strathy, if I have it correctly, that you hoped to obtain -- by you, the hospital hoped to obtain funding to permit that method to be tested for digoxin assays in the future, is that correct?
 - A. That's correct.
- Q. Dr. Ellis told us yesterday in evidence, Dr. Soldin, while I believe you were in the courtroom, that to his knowledge I believe he didn't think there was anybody in Canada who had experience in using the MS system for the



purposes of digoxin assays. Does that accord with your knowledge of the circumstances?

A. Dr. Kuksisx at the Best
Institute has certainly had experience with MS with
some of the digoxin compounds. Now, whether it is in
fact digitoxin or other metabolites, I cannot tell
you. It may well not be digoxin. He's had
experience with a number of very similar compounds.

- Q. All right. And is his experience with HPLC and MS as a combination technique?
 - A. Well, it wasn't three weeks ago
- Q. All right. Well, one can only be so definite, I suppose, sitting here today, Dr. Soldin.
 - A. Yes.
- Q. Can you help me with this.

 During the period July, 1980 to March of 1981

 and for the balance of 1981, to your knowledge, was
 there any laboratory of which you were aware that
 was using HPLC in combination with the MS
 methodology for the purposes of doing digoxin
 assays?
 - A. No, there wasn't.
- Q. All right. To your knowledge, was the HPLC MS technique, in terms of its hardware



and its	design	available	commerc:	ially	on the	
market	for dig	oxin assay	s during	that	period	of
time?						

- A. Yes, it was.
- Q. Can you help me as to when it became available for that purpose?

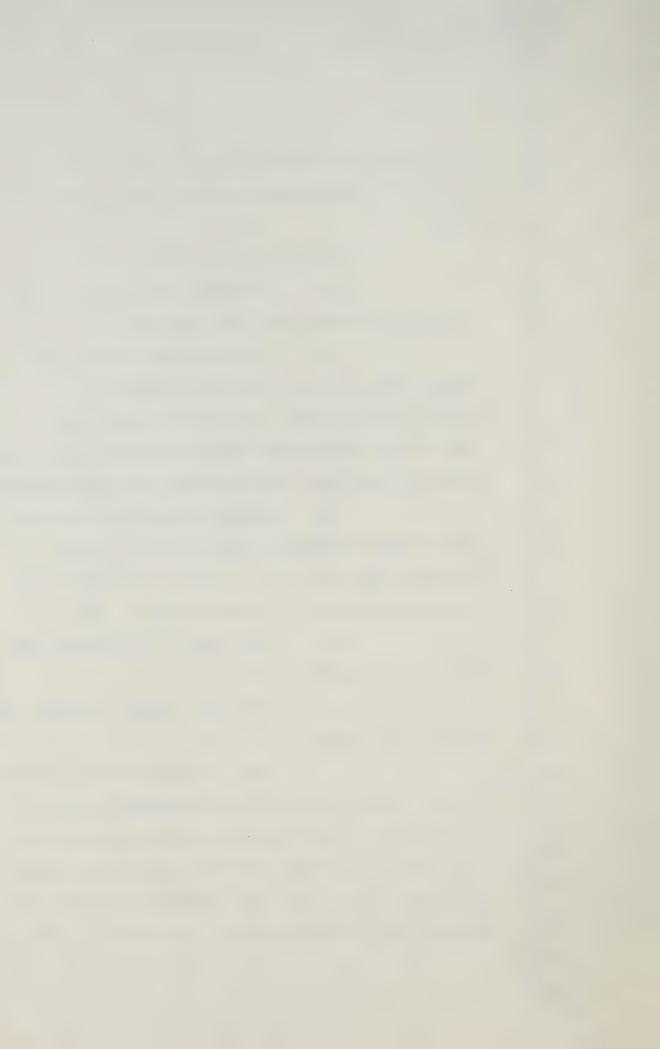
A. I would refer you to the system that is at the Best Institute is a Hewlitt Packard model, and HPLC/MS system and maybe if you phoned the Hewlitt Packard people they could tell you when that procedure was first introduced.

Now, I personally went and visited their plant in California around '79. It was certainly there in '79. It might have been there a few years earlier. It was newish in '79.

Q. And again -- I'm sorry, sir, have you finished?

A. The best thing is to ask them for the exact date.

Q. Well, perhaps we will do that in the future, but for present purposes so that I am clear as to your knowledge of the circumstances, I am talking now about the HPLC and MS combination for digoxin assays and your understanding that that was available commercially on the market in 1979.



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A. That's my understanding, yes.

Q. All right.

A. And possibly earlier.

Q. And possibly earlier.

A. Yes.

Q. But at that time, to your knowledge, there were no laboratories which you can identify for us that had acquired it and were using it for digoxin assay purposes?

A. Right.

Q. Thank you. You were questioned as well this morning, Dr. Soldin, again, by Mr. Strathy concerning the ability of the HPLC method to extract what's been called substance X and, if I understood the exchange correctly, it was suggested to you that it had not been possible to date to say with certainty that substance X was separated following an HPLC, the use of the HPLC methodology. Did I have that correctly?

A. I think that's correct.

I have just one rider on that and that is, I'm not sure what Dr. Gault is up to in Newfoundland.

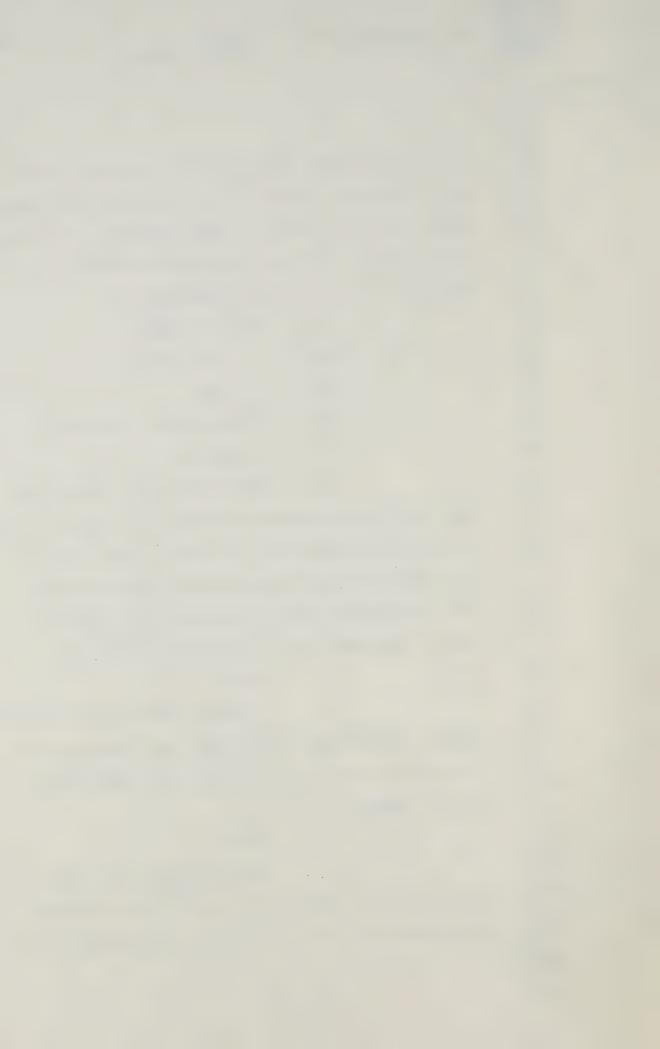
So, he may well have done some work in this area.

O. Well, bearing that in mind, would it be a fairer suggestion by me, Dr. Soldin,



to suggest to you that given the state of the art as it currently exists and the state of the research as has been described in these hearings, it cannot with certainty be said today that the HPLC method does not in fact separate substance X.

- A. That's right.
- Q. It may separate it?
- A. It may.
- Q. Then again it may not?
- A. Correct.
- Q. And would I be correct as well or fair in suggesting that on the state of the research as it has been described to us, that in any given sampling group that is run through an HPLC methodology for the purposes of a digoxin assay, substance X may or may not be present?
 - A. Right.
- Q. In fact, there would be some sample groups borne out by your own experience at the hospital that would suggest that substance X was not there.
 - A. Right.
- Q. Dealing again with the questions that were put to you by varous counsel concerning the, if I can express it this way, the



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yes.

utility of one digoxin assay methodology as compared with another, would you agree with me, Dr. Soldin, that any scientist, if required to recreate or implement from scratch a methodology for the purposes of conducting digoxin assays, would bring to bear on that problem in settling upon his

A. Right.

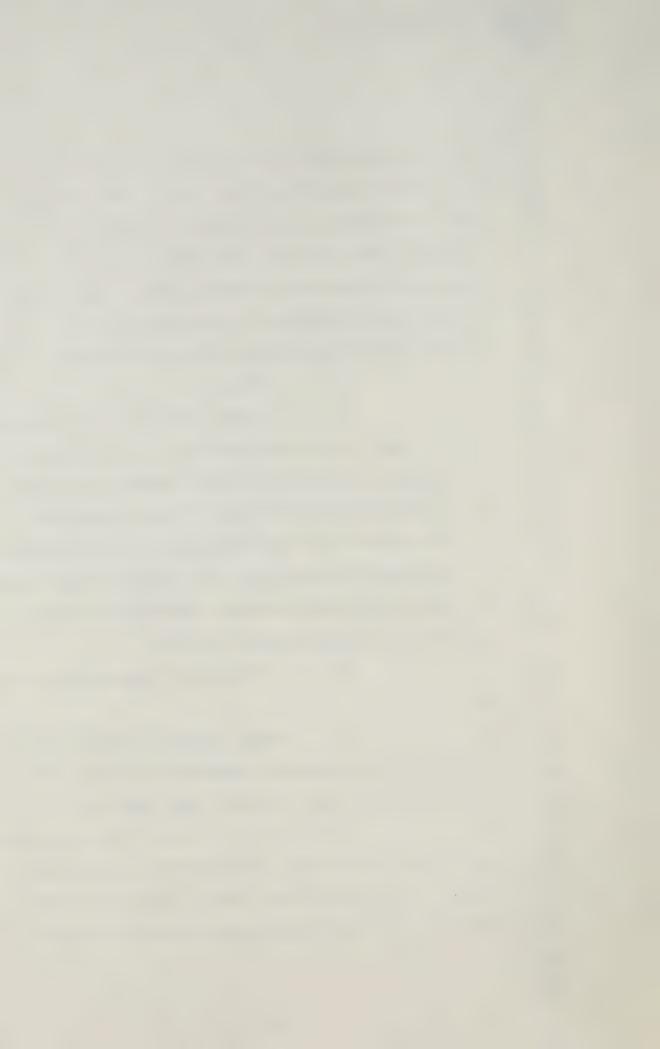
methodology his experience with other assays?

Q. Right. Would you also agree with me that if the scientist that I am proposing was creating from scratch such a system and he had 20 or 30 years or 10 years or 15 years experience in using particular kinds of assays for the purposes of recording or determining drug concentration levels, he would bring that practical experience to bear on the decision making process as well?

A. He would be tempted to do that,

Q. Well, would a prudent scientist not rely on the practical experience that he had accumulated over the years in making that decision?

A. Yes, he would. That would be part of his evaluation. He would have to consider whether or not there were newer or better methods available and then make a value judgment on which



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which to go.

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0. Yes. And exactly on that point, you would agree with me, I take it, that there is an element of professional judgment that enters into the exercise?

> There certainly is, yes. Α.

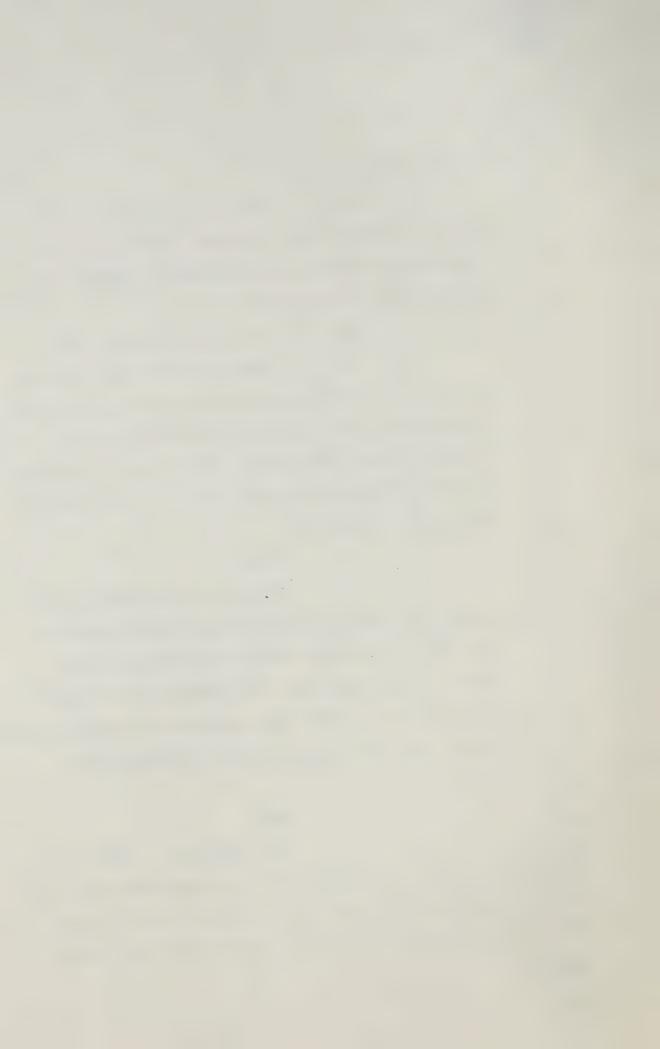
0. And would you agree with me as well that the scientist creating or implementing from scratch, if I can use that colloquialism, a digoxin assay methodology would also, if prudent, bear in mind the purpose to which the test results were likely to be put?

> Yes. A.

So that if a clinical biochemist or clinical pharmacologist were asked or required to implement such a system for digoxin assays in your hospital, for example, if prudent he would bear in mind the therapeutic drug monitoring purpose that was associated with creating that assay?

> Α. Yes.

0. And similarly, a forensic scientist, if required to create and implement such a methodology, would bear in mind that in certain circumstances there was a likelihood that test





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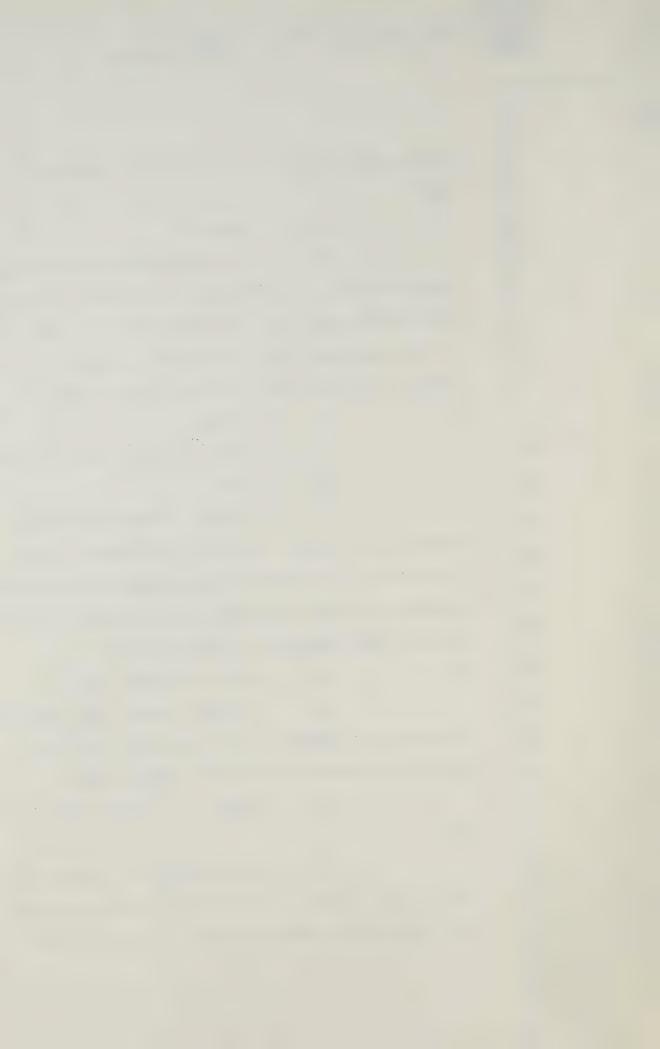
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results might bear the scrutiny of a court of law?

- Α. Correct.
- 0. In questioning this morning from Ms. Kitely, Dr. Soldin, you showed to her a slide indicating, as I had understood it, the optimum sampling time for taking a sample of digoxin. Do you recall showing that slide?
 - Α. Right.
 - And explaining what it meant? 0.
 - Α. Yes.
- 0. And as I understood your evidence, if I made a note of it correctly, you indicated that the best time for many drugs to take a sample for assay purposes was just before the next dose was administered, is that correct?
 - Α. That's correct, yes.
- Right. And we know from your evidence that digoxin at the Hospital for Sick Children is administered every twelve hours.
 - Mostly. I believe that to be Α.
- 0. Well, perhaps I phrased it badly. As a matter of routine it is anticipated that digoxin was administered to those patients



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prescribed digoxin once every twelve hours.

A. Yes, and a study is currently in progress to evaluate whether or not we should be changing that to every 24 hours.

Q. All right. Well, the difficulty that I am having, Dr. Soldin, for the
purposes of clarification is this: we know from
the contents of the Residents' Handbook that we had
examined previously, that at Page 365 of the handbook
it is indicated that the optimum, perhaps the word
optimum isn't used, but the time for the sampling
of digoxin is indicated to be between six and eight
hours after administration, is that correct?

A. Yes.





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Q. Is it then to be taken by us that the optimum time for sampling, for taking a sample for digoxin assay is anywhere after six hours up to and inclusive of the eleventh hour prior to the administration of the next dose?

A. No. My opinion is that the optimal time is just before the next dose. The six-hour post dose sample is adequate, but it is not optimal.

Q. So the six-hour time frame I take it then, in your judgment would be the first onset of the steady state?

A. Right.

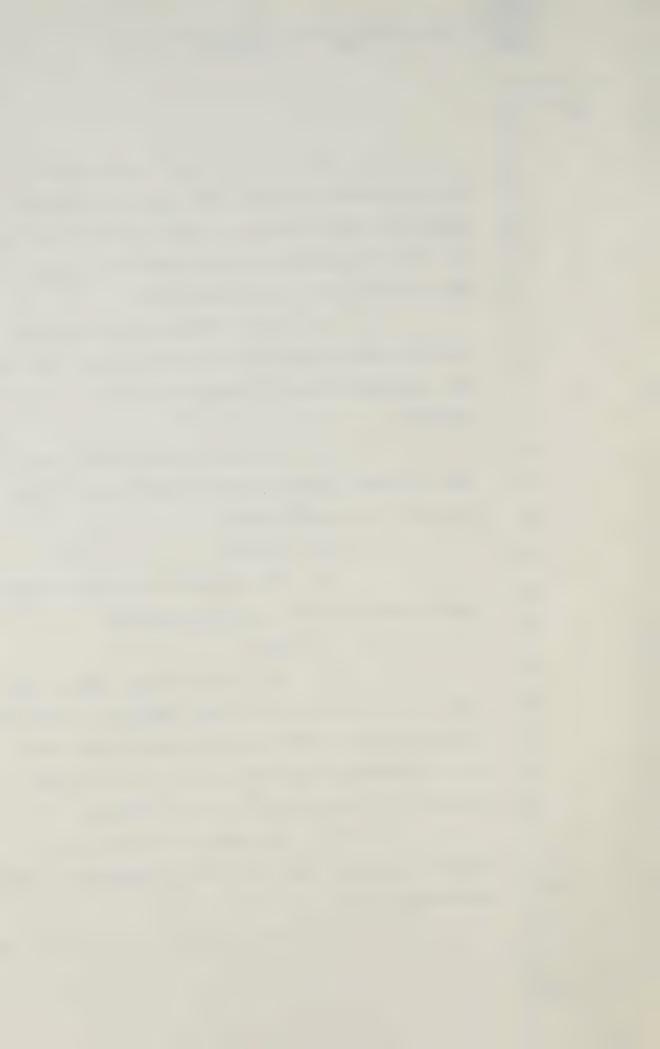
Q. The earlist time which a sample might safely be taken, is that correct?

A. Yes.

Q. Am I correct then that at any time after six hours up to and inclusive of the very minute before the next dose is administered would be an acceptable time frame within which to take a sample for digoxin assay, in your judgment?

A. In order to interpret the result clinically and make certain judgments on that measurement, yes.

Q. Do I correctly take it from that





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then that the steady state which is introduced at the earliest of the sixth hour after administration of the dose, continues on the same plane for the next six hours until the next dose is administered?

You have used I think the wrong term. It is not the steady state, it is an equilibrium that is achieved after the six hours. The steady state concentration was on the other slide and that takes five half lives to achieve for a drug that is given at intervals equal to its half life, approximately five half lives.

Perhaps I have confused the two concepts. My point is this, is there any danger after the sixth hour, after the administration of the dose of digoxin, if one were to take a sample at the tenth hour, or the eleventh hour, is there any danger of further peaking in concentration of the drug, or would a sample taken at any time within that range be acceptable for your purposes on a digoxin assay?

In the routine management of patients that are receiving digoxin orally, a six-hour post dose sample would be adequate, but not optimal. It is possible that if a patient, as in one of our cases several weeks ago, they had swallowed a large number



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of somebody else's tablets.

0. Yes.

That the concentration may continue to rise for quite some time and indeed it did in that patient. But that is an abnormal situation and not one that is usually present.

Are you saying then, Doctor, in certain abnormal or isolated situations the drug may continue to peak after six hours?

The concentration in this particular patient remained elevated for a long time. Now, I can't tell you because I don't have the graph in front of me when it actually peaked. This was a patient that had taken oral digoxin tablets and a large number of them.

Then returning to your earlier view as I have understood you to express it, and correct me if I am wrong. I understood you to say that in your judgment the optimum time for the taking of the sample for digoxin assay is the hour before the next dose is administered?

In a routine therapeutic drug monitoring setting, yes, not in a toxicology setting.

So that is something we should bear in mind in reviewing the contents of the Handbook?





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Yes. A.

0. You will recall as well, Dr. Soldin, that in your discussions this morning you offered your opinion, as requested, with respect to a number of the procedures followed, adopted by Mr. Cimbura in conducting digoxin assays. You spoke about his extraction process and the standards that you understood he had used.

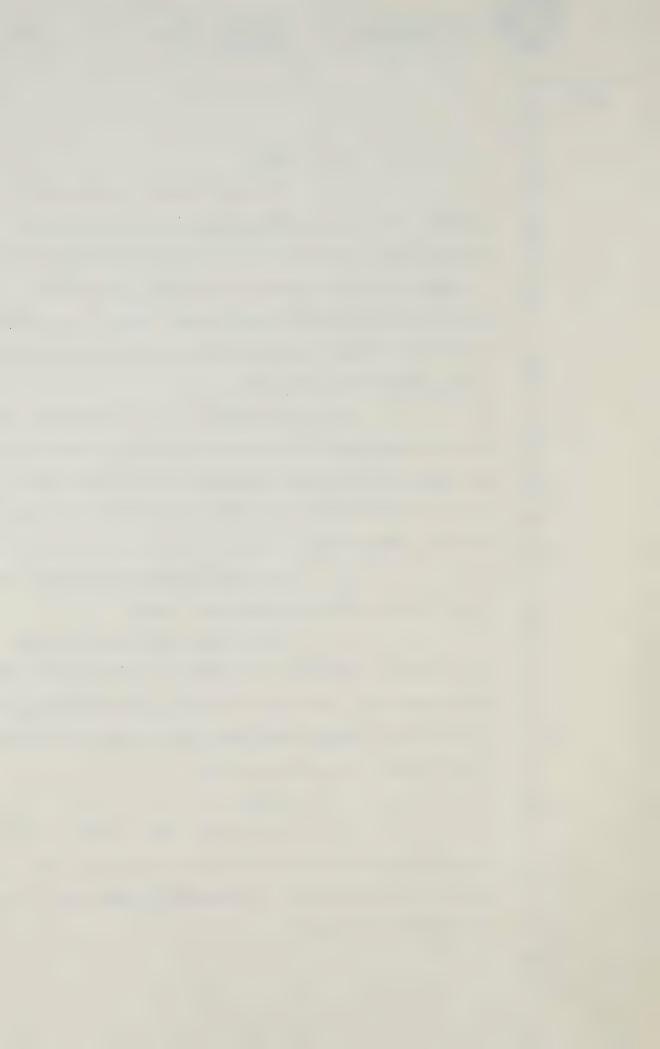
Dr. Ellis told us in his evidence that in his laboratory in running RIA digoxin assays that he did not use an extraction process on the sample once he received it. Is that the practice as well in your laboratory?

We use a protein precipitation step not an extraction process, right.

Let's take that step by step. You told me previously that with respect to the FPIA technique that there was a protein precipitator, or a separation process that was part of the methodology that worked on the FPIA system?

Right.

Let's talk about first the RIA 0. assays that you have run in your laboratory. respect of those have you adopted or made use of an extraction process?





A. No.

Q. In respect of the FPIA digoxin assays that you have run, and apart from the protein precipitator component of the process that you previously described, do you make use or have you adopted an extraction process?

A. No.

Q Dr. Ellis also told us in his testimony Dr. Soldin, that if he were required or provided an opportunity to modify the Hospital's RIA methodology for the purposes of conducting post mortem digoxin assays, that one of the things that might be included as a modification was an extraction process.

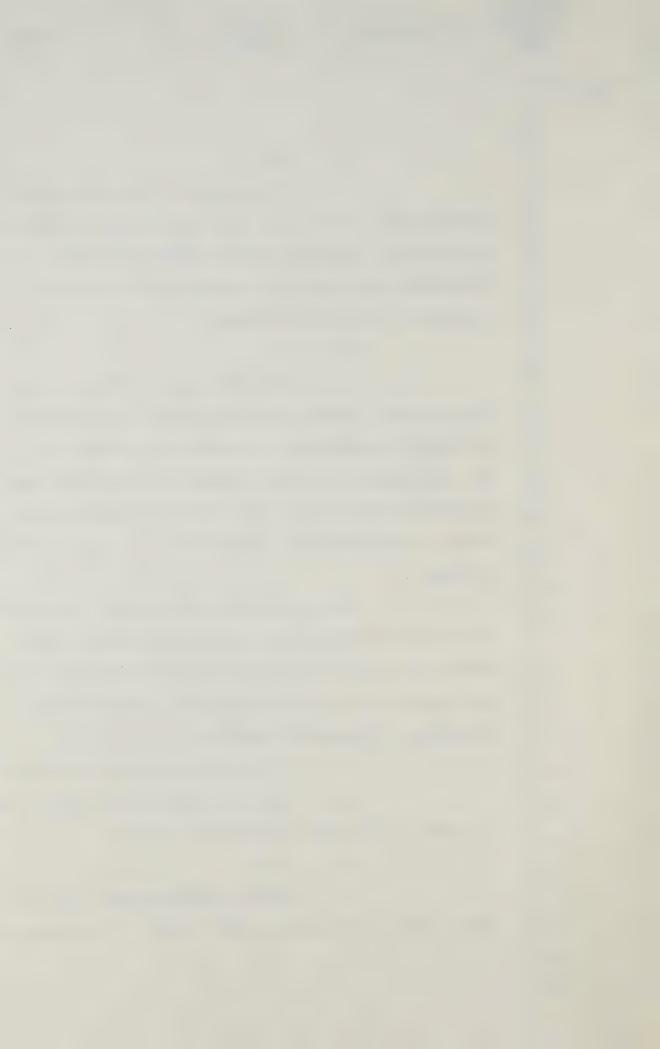
Do you agree, based on your experience with both methodologies, that if one were to adopt either for the purposes of post mortem testing, that you would look to the inclusion of the extraction process as a desirable component?

A. It may be a desirable component.

Q. That is something you would want to look at and make a determination on?

A. Right.

Q. And do you agree with me, and again I may be expressing this poorly or inadequately





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and if so I would like you to tell me. My understanding of the process, of the extraction process that is utilized by Mr. Cimbura was for the purposes of separating out digoxin metabolites. Does that accord with your understanding of the process he described?

Well, he might have used that extraction to separate or to attempt to separate any compounds that would interfere with the digoxin reacting with the antibody. In other words ---

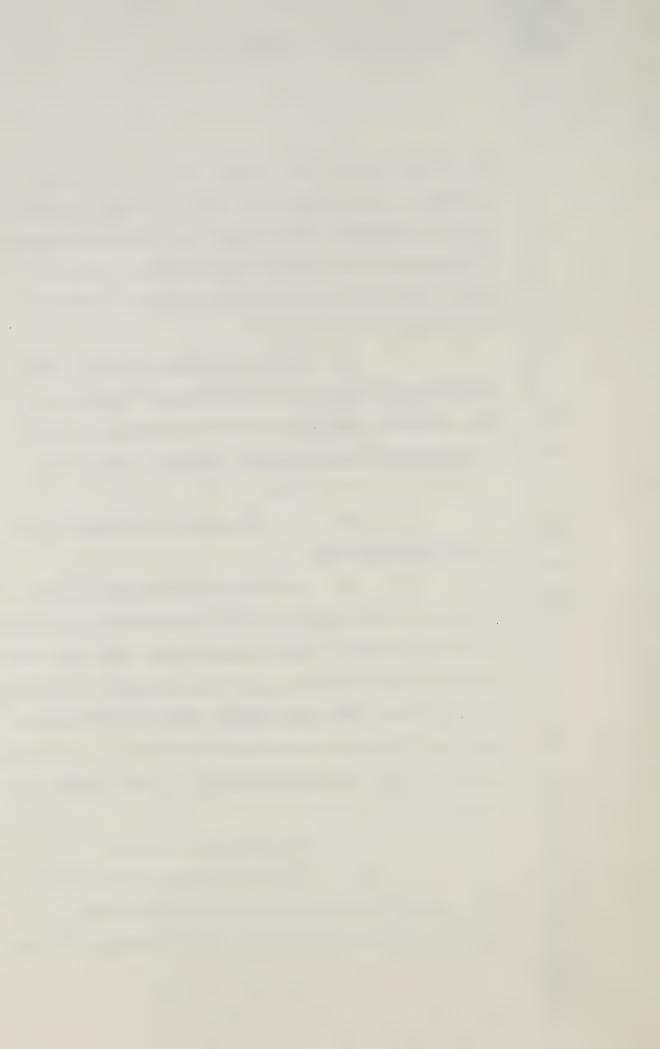
> 0. Yes.

-- and need not necessarily be digoxin metabolites.

To put it another way if the purpose of using the extraction process is to achieve in the end result a purer sample upon which the assay might be run, would you agree with me that if one were satisfied as to the particular extraction process at hand that would be a desirable end, that is something you would like to achieve before in fact running an assay?

> In a forensic setting. A.

I am not asking you to comment on a setting with which you have no experience. your own setting if you were - the proposition I put





to you was that if you were to moderate or modify either methodology currently in use in the Hospital, be it the RIA methodology or the FPIA methodology, for the purposes of running post mortem digoxin assays, in your judgment would it be a desirable end to introduce an extraction process?

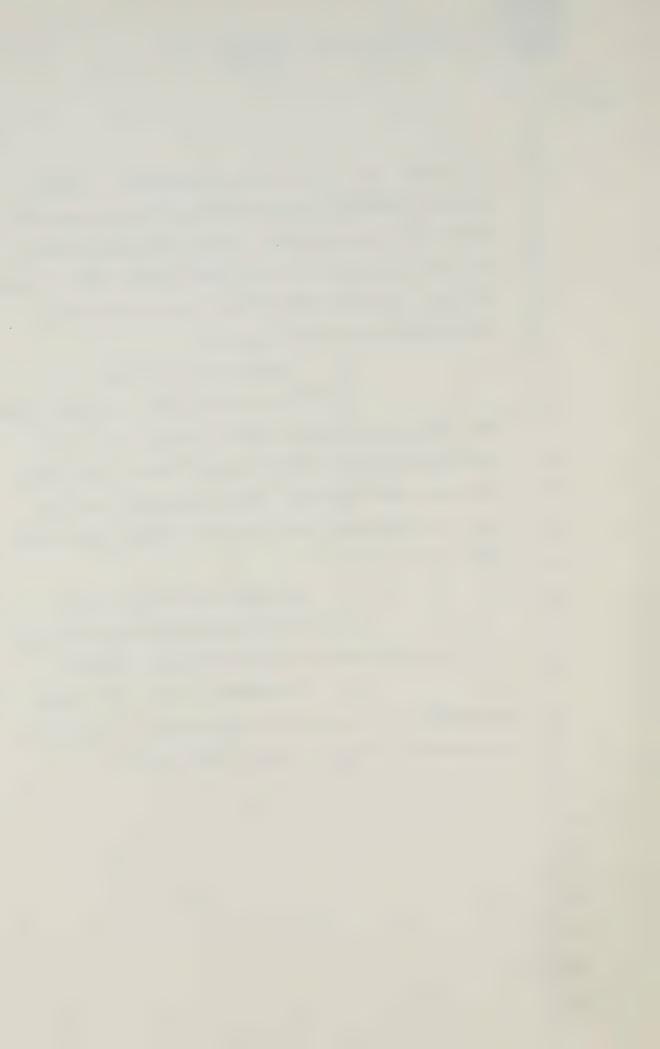
A. I would evaluate that.

Q. I am asking you in general terms now, the purpose of the extraction process is to achieve in the end result a purer sample upon which the assay might be run. Would you agree with me that in conceptual terms that is a highly desirable end?

A. It may be desirable, yes.

Q. It is not necessarily something that one would seek to achieve from the outset?

A. It depends on what the method of measurement is going to be subsequently, it may not be necessary, it may be and it may not be.



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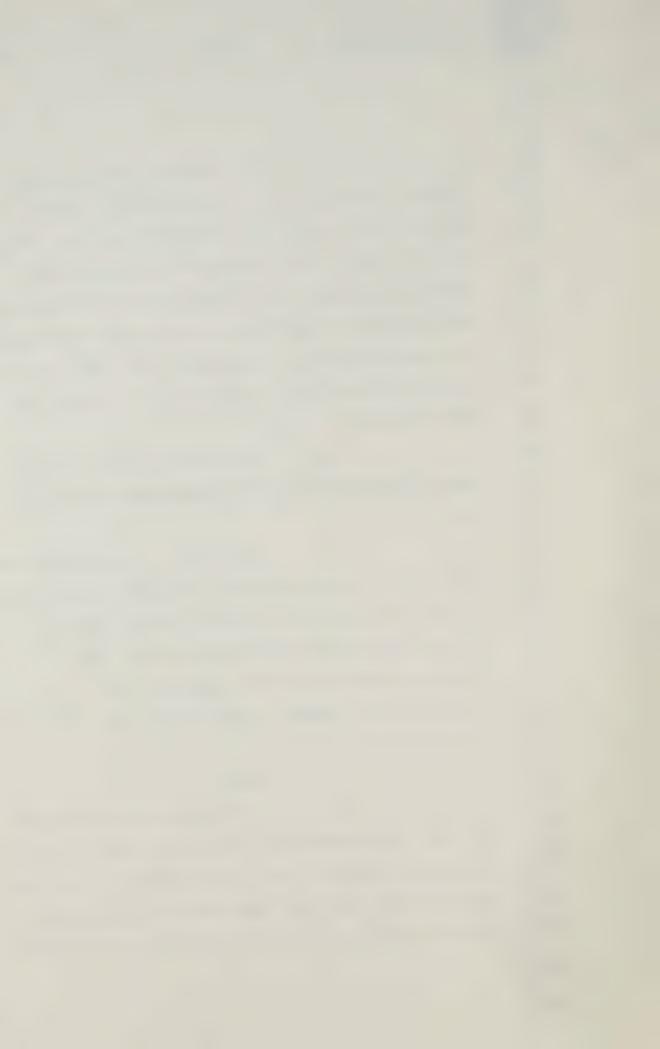
Q. Dr. Soldin, dealing again with the process that we have heard Mr. Cimbura used for his testing, and I would like to be clear on this and in light of some of the answers you gave this morning. As I understand it, in conducting the RIA digoxin assay test that you have conducted or supervised in your laboratory, you have not had occasion to make use of the Beckman antibody, is that correct?

A. I have personally not, but one of the post-doctoral fellows working with me, have.

Q. I'm sorry, I perhaps put the question in a confusing way. You told me previously in your evidence that a post-doctorate candidate working under your supervision had used the Beckman antibody with the system that you understood Mr. Cimbura to have been using, his methodology?

A. Right.

Q. I am talking now about your own, the RIA methodology that was used and is used in your laboratory. Am I correct that you have not had occasion, nor have those whom you supervised, to use Beckman antibody as part of your RIA process,



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is that correct?

I have had occasion, but Α.

I haven't done it.

Again, it has not been done? Q.

No. Α.

Neither by yourself nor by Q. anyone under your supervision.

Right.

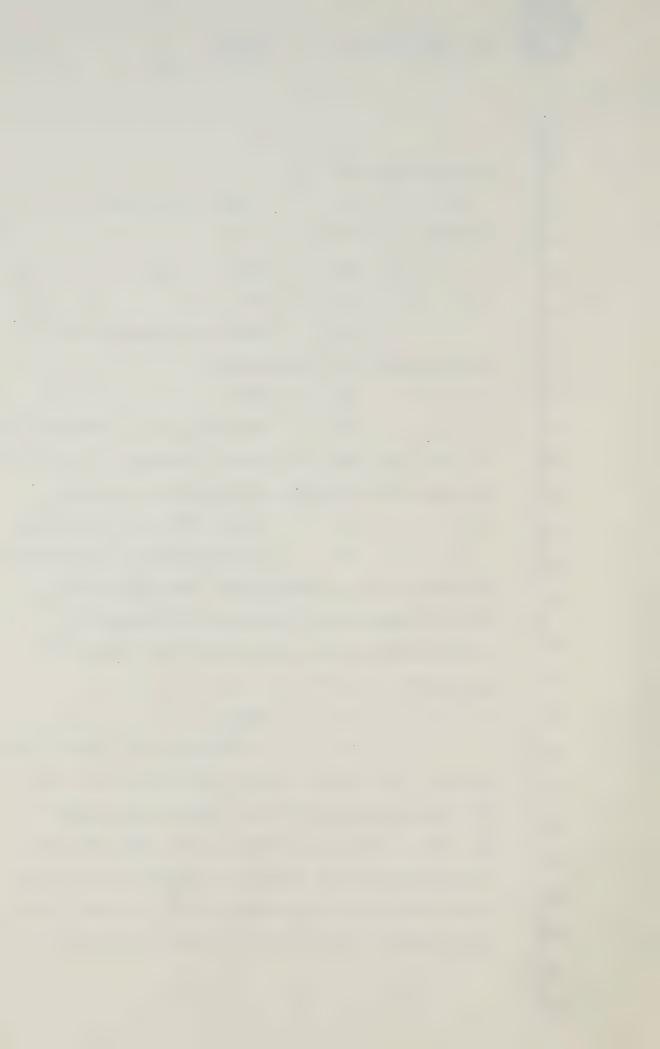
Similarly, as I understand it, you have not used the Beckman standards in your RIA process nor has anyone under your supervision.

In our RIA process, correct.

And, of course, neither would be used by you or those under your supervision in the FPIA methodology because the standards and the antibodies that are used on that system are provided by others?

A. Right.

In questions put to you this morning, Dr. Soldin, again, with respect to the RIA methodology used by Mr. Cimbura as opposed to the one in use at the Hospital for Sick Children, questions were put to you as to whether or not you could afford any explanation as to the time frame, the length of time that Mr. Cimbura indicated it took





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for him to conduct a test using the methodology that he had formulated.

Comparing the RIA Methodology that has been described here as in use at the hospital with what you understood to be the case from Mr. Cimbura's evidence, the methodology he used, would you agree with me that the length of time that it takes to run an RIA assay would be increased first if an extraction process was used?

Yes.

And would you agree with me that it would be increased in length of time, secondly, if the gamma counter that you are using to calculate the amount of bound digoxin as opposed to the amount of unbound digoxin was not capable of doing readings on more than one sample at one time?

> Α. Yes.

Would you agree with me that the length of time would be increased again if it was considered desireable or proper technique, to leave the gamma counter with the samples sitting over-night to arrive at a calculation the next day that would necessarily increase the length of time?

> Α. Yes, that would increase the



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length of time, and it may or may not improve the results.

Q. It would increase the length of time if that step were undertaken.

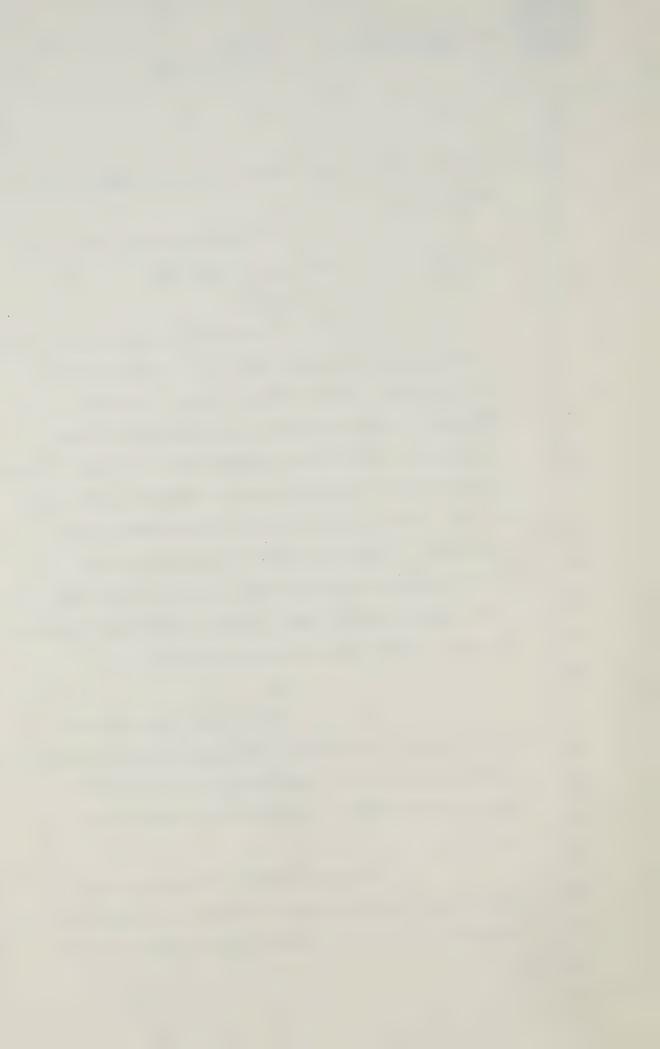
A. Yes

a fair suggestion to you that if a tissue sample were received, and I recognize and I am very sensitive to your lack of experience with tissue testing, but if a tissue sample were received for the purposes of the digoxin assay, would you agree with me that there might be special procedures which would have to be undertaken in respect of the tissue sample before the assay could be run that might again increase the length of time that it would take to run the assay in its entirety?

A. Yes.

Q. And mention was also made this morning, Dr. Soldin, of testing on whole blood. I believe this was a question put to you by Ms. Jackman and, again, I wanted to be clear about that.

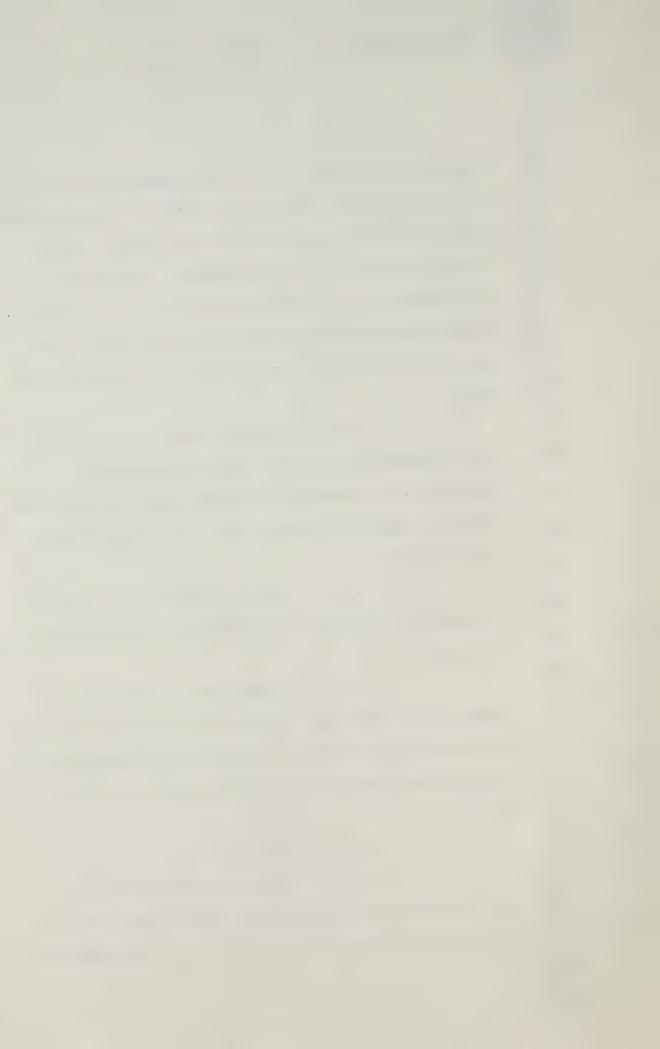
Would you agree with me, taking into account your previous evidence, that digoxin assays are not run on whole blood samples at the



Hospital, certainly not in your laboratory and not in Dr. Ellis' laboratory. Bearing that in mind, would you agree with me once again that if in a forensic setting it was considered desirable or necessary that digoxin assays be run on whole blood samples, that there may be procedures that apply in respect of -- I am sorry, I expressed that badly.

Is it, in your view, possible that in a forensic setting it could be considered desirable or necessary for digoxin assays to be run on whole blood, or can you offer us an opinion in that regard?

- A. It is feasible that may be an important analysis on whole blood in a forensic setting.
- Q. I believe you indicated in response to questions earlier this morning that you had personally noted in the forensic literature that they mainly referred to digoxin assays on whole blood.
 - A. Correct.
- Q. Finally, Dr. Soldin, you will recall that in questions put to you by my friend, Mr. Ortved, this morning it was suggested



one should take into account in running digoxin assays, and of those mentioned were the time of the last dose; the site from which the particular samples had been taken; the method of administration of the dose; the age of the patient; whether the sample was ante mortem or post mortem. Do you recall those factors being put to you this morning?

Yes.

Α.









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Q. Would you agree with me,
Dr. Soldin, that for the purposes of running the
digoxin assayitself, for the purposes of utilizing
the methodology to arrive at a recording which as a
scientist you felt was acceptable in terms of
accuracy on the methodology itself, that those
factors are irrelevant?

- A. I beg your pardon?
- Q. All right.

THE COMMISSIONER: Yes, Mr. Strathy?

MR. STRATHY: Mr. Commissioner, I

know that we are not bound by the rules of evidence here, but it seems to me that perhaps there ought to be some distinction between the nature of the questions put by Commission Counsel and the nature of the questions put in cross-examination by other counsel.

THE COMMISSIONER: Yes. There may be something to what you say, but when we get around to re-examination, the temptation to lead is almost overwhelming.

MS. CRONK: And for some of us it appears it is overwhelming, Mr. Commissioner.

If I can help my friend, perhaps I will re-phrase it in a less leading fashion.

MR. STRATHY: I think sometimes for



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the witness himself it may be better to hear it in the witness' own words. I appreciate what Miss Cronk is trying to do in terms of saving time.

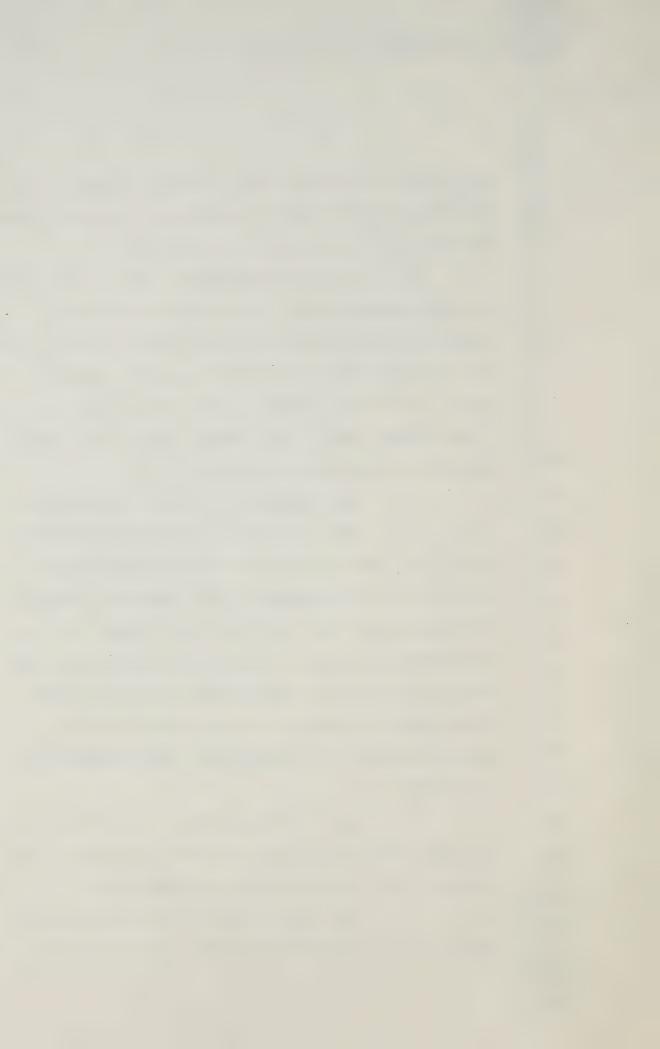
THE COMMISSIONER: Yes. Just, have you any comments upon - can we put it this way forget everything you have heard today, can you just tell us if you have any comment upon Mr. Ortved's list. He had only seven. I put down eight, but I sub-divided one of his. Eight matters that would require caution in the testing.

THE WITNESS: Right. No comment.

MS. CRONK: Q. Without offending either you, sir, in terms of the proper manner in which to put the question or my friend Mr. Strathy or others, can I ask you this, Dr. Soldin? In your professional judgment is the time at which the last dose of the drug is administered relevant to the conducting of a digoxin assay as opposed to the interpretation of the results of the recording and, if so, how?

Are you asking me if the time Α. at which the drug is administered - relative to the sampling time, that is certainly important.

All right. And similarly with 0. respect to - is knowing the site from which the



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sample has been taken relevant to you in conducting the digoxin assay?

- A. In a routine monitoring lab?
- Q. Yes.
- A. Whether the sample is from a heel prick or a finger stab or a vena puncture, it doesn't make any difference.

THE COMMISSIONER: The only point surely in all of this is that you are saying that it doesn't affect his ability to do the test, but the results will be somewhat different. Isn't that the point?

MS. CRONK: That is certainly the point, Mr. Commissioner.

THE COMMISSIONER: If it is of any help to you, it is a point that I have already mastered.

MS. CRONK: That's the best possible answer to the question that I could have received, Mr. Commissioner.

THE WITNESS: Well now, I don't agree with the answer.

MS. CRONK: 'Apparently we have some disagreement.

THE COMMISSIONER: That's why I



wanted your comments, all right.

THE WITNESS: There is no evidence that I'm aware of whether one gets the sample from a finger prick, a finger stab or a vena puncture the digoxin measurement will be different.

MS. CRONK: Q. Are we clear on at least this, Dr. Soldin, that you are not involved in the interpretation of the results that you achieve on your digoxin assays?

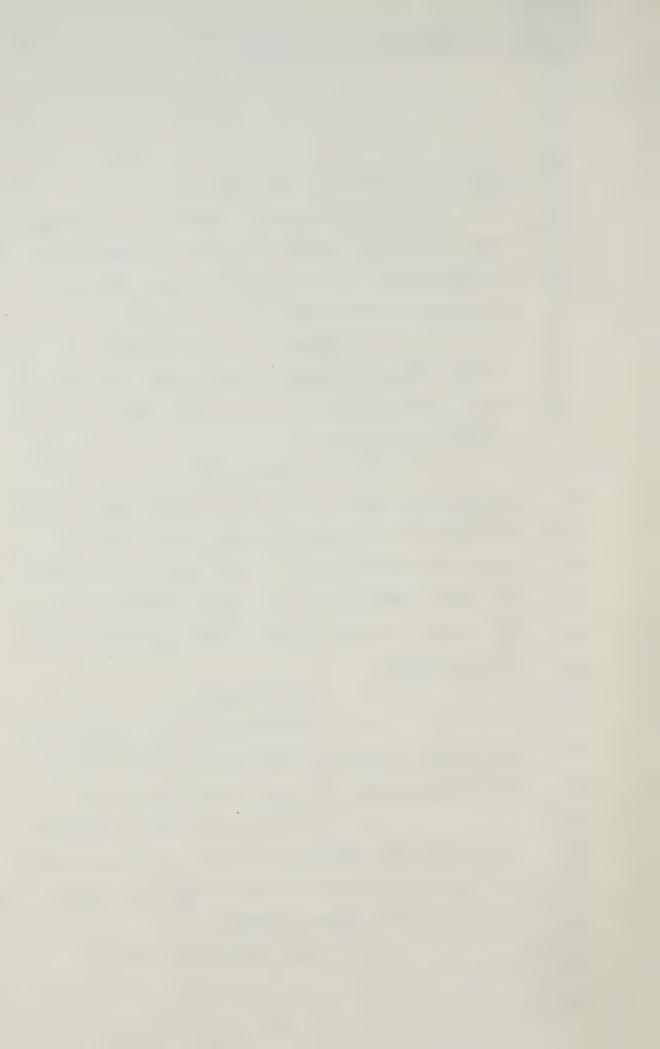
A. To some extent I'm involved because when results are over a certain level I have to notify the right people and my group have to notify the right people. I don't go to the bedside and look at the patient and decide whether or not the patient is toxic. That is done by the clinical pharmacologists.

Q. That's right.

A. And the clinicians looking after the patient. But it is my responsibility to be sure that a message gets to these clinicians quickly.

Q. And can we go this far together,
Dr. Soldin, that there are a number of factors which
are highly relevant to the cardiologist in interpreting
the results of a digoxin assay?

A. Highly relevant, yes.



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Q. That are not relevant to you in conducting the test.

THE COMMISSIONER: I'm sorry?

THE WITNESS: Well, it depends which factors you are talking about. If the sample for example, is drawn at an inappropriate time then it's relevant to me and the test should not be performed. I am wasting the Province's funding by performing a test when the result cannot be interpreted.

MS. CRONK: I think, Dr. Soldin, and with the Commissioner's concurrence, I will leave the point there. Thank you.

> THE COMMISSIONER: Yes.

MS. CRONK: No further questions.

THE COMMISSIONER: Thank you.

If you are wise, you will make a hasty retreat before somebody else gets at you, Dr. Soldin. Thank you very much.

THE WITNESS: Thank you.

---Witness withdraws.

THE COMMISSIONER: Have you anything further, Mr. Lamek?

MR. LAMEK: I thought you were inviting me to cross-examine Dr. Soldin.

THE COMMISSIONER: No, no I am not.





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MR. LAMEK: Nothing further today then, Mr. Commissioner.

THE COMMISSIONER: All right. Well then, until Tuesday at 10 o'clock.

MS. CRONK: Thank you, sir.

MS. KITELY: Mr. Commissioner,

before we rise. At the risk of asking too much of Commission Counsel, I know that we are going to hear from the cardiologist next.

THE COMMISSIONER: No, I think we are hearing from the mortician.

MS. KITELY: Yes, and then the cardiologist. But I rise to ask if Mr. Lamek has any long term plans he can let us in on. My concern is that if the nurses, for example, are going to follow the doctors, then we would like to know that in terms of timing. If he has other witnesses that he's going to stick in before he gets to another client, I want to know that. I know that I can't pin him down to the date and the time, but a general frame of reference would be helpful.

THE COMMISSIONER: Well, he gave a sort of a program at the beginning, the agenda.

MR. LAMEK: Yes, I thought I had tried to do that, but let me reply. I do not



anticipate, I do not expect to call any nurse as a witness for at least four or five weeks. I propose to lead all of the medical evidence on the charts and perhaps the evidence of clinical pharmacologists and of course the evidence as to the particular digoxin measurements, the evidence of clinical pharmacologists as to the significance of those measurements in those cases and those children and then of course we have to call the authors of the Atlanta Report.

Miss Kitely may be assured that her clients are well away from the witness box at this point, many weeks I'm afraid. All that has to be done before I even think of calling a nurse as a witness, Mr. Commissioner.

MS. KITELY: Thank you, sir.

THE COMMISSIONER: Yes, all right.

I suppose we could mention that we are giving some thought to moving also but I think that will not be until - obviously we will not be able to keep these premises past Labour Day and we now seem to have permission for the large court room at 180 Dundas Street. It is the Ontario Municipal Board place at 180 Dundas and we may be going there some time in August. So, that is an advance warning.



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If you some day come here and find nothing is going on, it doesn't mean that the Inquiry is completed.

MR. LAMEK: Mr. Commissioner, a rider that if you find nothing is going on and no one is here.

---Whereupon the hearing adjourned at 2:35 p.m. until Tuesday, July 12th, 1983 at 10:00 a.m.



